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(54) Title: COMPOSITION CONTAINING AMINE AND AMINE-RELATED DERIVATIVES OF BENZOIC ACID AND USES THEREFOR INCLUDING TREATING INFLAMMATORY DISEASES

(57) Abstract

The invention is drawn to a novel composition containing amine and amine-related derivatives of benzoic acid and uses therefor including treating inflammatory diseases.

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Composition containing amine and amine-related derivatives of benzoic acid and uses therefor including treating inflammatory diseases

I. SUMMARY OF THE INVENTION

The present invention is directed to the use of compositions consisting of amine and amine-related benzoic acid derivative primary agents capable of covalently binding carbonyl substances and co-agents consisting of antioxidants, free radical trapping substances, vitamins and vitamin-related substances, for use in the treatment of symptoms of chronic inflammatory disorders, said disorders featuring oxidative free radical reactions, lipid peroxidation and generation of carbonyl compounds as aspects of their etiologies.

The invention relates to the use of a composition comprising a therapeutically effective amount of a primary agent and at least one co-agent, said primary agent comprising a water soluble, low molecular weight primary amine or amine-related derivative of benzoic acid in the molecular weight range of 100 to 1,400, for use in the treatment of symptoms of chronic inflammatory disorders featuring pathology based in part on increased lipid peroxidation, wherein said primary and co-agent combination produces an anti-inflammatory and analgesic effect.

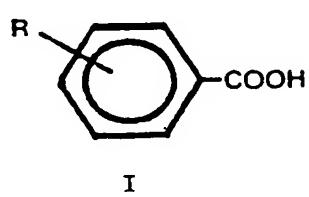
In such a preferred embodiment of the use of a composition comprising a therapeutically effective amount of a primary agent and at least one co-agent for treatment of the symptomatology of a chronic inflammatory disease, the chronic inflammatory disease is characterized in part by the deterioration of intracellular and extracellular structures and is characterized by the spurious pathological chemical covalent bond crosslinking of

said structures, formation of pathological addition products of said structures, or chemical cleavage products of said structures, said deterioration resulting from reaction of inflammation site structures in the human with discase-induced carbonyl-containing aliphatic and aromatic hydrocarbons resulting from increased lipid peroxidation associated with chronic inflammation.

In a preferred embodiment of this aspect of the invention, the primary agent has at least one primary amino group or amine-related group theron for reaction with lipid peroxidation product carbonyl groups to decrease the deterioration of said intracellular and extracellular structures and to decrease the spurious pathological chemical crosslinking, other derivation or cleavage of said structures by permitting a therapeutically effective amount of said primary agent to effectively compete with and covalently bind to said discase-induced carbonyl-containing lipid peroxidation products.

In a preferred embodiment, the use of the primary agent is additionally characterized in that it does not interact with normal cell metabolism of said human or does so in a non-cytotoxic manner, and the primary agent is readily absorbed by the kidney tissue of said human and excreted in the urine of said human without nephrotoxic consequences.

In a preferred embodiment, the use of a water soluble primary agent of molecular weight in the range of 100 to 1,400 is selected from the group consisting of the free acid forms, salts, benzene ring isomers, amide derivatives, carboxylic acid ester derivatives and analogous non-aromatic benzene ring derivatives of the group consisting of:

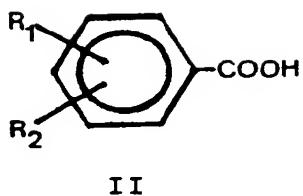


$R = -NH,$
 -aminoalkyl group having
 1-10 carbons including
 hydrocarbon isomers
 and/or hydroxylated
 derivatives thereof
 $-NHC(=NH)NH,$
 $-(CH_2)_nNHC(=NH)NH,$
 where $n = 1-10$
 $-C(=NH)-NH,$
 (continued)

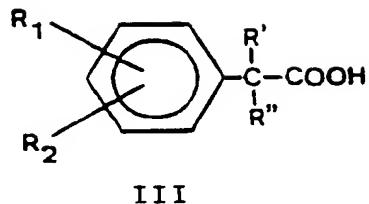
$-\text{CH}_2\text{CH}=\text{NC}(=\text{NH})\text{NH}_2$,
 where $n = 1-10$
 $-\text{NHC}(=\text{NH})\text{NHNH}_2$,
 $-\text{CH}_2\text{NHC}(=\text{NH})\text{NHNH}_2$,
 where $n = 1-10$
 $-\text{CH}_2\text{CH}=\text{NC}(=\text{NH})\text{NHNH}_2$,
 where $n = 1-10$
 $-\text{NHNHC}(=\text{NH})\text{NH}_2$,
 $-\text{CH}_2\text{NHNHC}(=\text{NH})\text{NH}_2$,
 where $n = 1-10$
 $-\text{CH}_2\text{CH}=\text{N}-\text{NHC}(=\text{NH})\text{NH}_2$,
 where $n = 1-10$

$\text{R}_1 =$ $-\text{NH}_2$
 $-\text{aminoalkyl group}$
 $(1-10 \text{ carbons})$
 $\text{including hydrocarbon}$
 isomers and/or
 hydroxylated
 $\text{derivatives thereof}$
 $-\text{CH}_2\text{NHC}(=\text{NH})\text{NH}_2$
 where $n = 1-10$
 $-\text{C}(=\text{NH})-\text{NH}_2$,
 $-\text{CH}_2\text{CH}=\text{NC}(=\text{NH})\text{NH}_2$,
 where $n = 1-10$
 $-\text{NHC}(=\text{NH})\text{NHNH}_2$,
 $-\text{CH}_2\text{NHC}(=\text{NH})\text{NHNH}_2$,
 where $n = 1-10$
 $-\text{CH}_2\text{CH}=\text{NC}(=\text{NH})\text{NHNH}_2$,
 where $n = 1-10$
 $-\text{NHNHC}(=\text{NH})\text{NH}_2$,
 $-\text{CH}_2\text{NHNHC}(=\text{NH})\text{NH}_2$,
 where $n = 1-10$
 $-\text{CH}_2\text{CH}=\text{N}-\text{NHC}(=\text{NH})\text{NH}_2$,
 where $n = 1-10$

$\text{R}_2 =$ $-\text{NH}_2$
 $-\text{OH}$
 $-\text{O-CH}_3$
 $-\text{O-R}' \text{ with alkyl oxy}$
 $\text{group R' having 2-10}$
 carbons including
 $\text{hydrocarbon isomers}$
 $\text{and/or hydroxylated}$
 $\text{derivatives thereof}$
 $-\text{aminoalkyl group}$
 $(1-10 \text{ carbons})$
 $\text{including hydrocarbon}$
 isomers and/or
 hydroxylated
 $\text{derivatives thereof}$
 $-\text{SO}_3\text{H}$
 $-\text{CH}_3$
 $-\text{CH}_2\text{CH}_3$ where $n = 1-10$
 $\text{including hydrocarbon}$
 (continued)



isomers and/or
hydroxylated
derivatives thereof



$R_1 = -(CH_2)_n-NH_2$ where $n = 0-10$
including isomers of
the aminoalkyl group
and hydroxylated
derivatives thereof
-C(=NH)-NH,
-NHC(=NH)NH,
-(CH₂)_nNHC(=NH)NH,
where $n = 1-10$
-(CH₂)_n-CH=NC(=NH)NH₂
where $n = 1-10$
-NHC(=NH)NHNH,
-(CH₂)_nNHC(=NH)NHNH₂
where $n = 1-10$
-(CH₂)_n-CH=NC(=NH)NHNH₂
where $n = 1-10$
-NNHNC(=NH)NH₂
-(CH₂)_n-NNHNC(=NH)NH₂
where $n = 1-10$
-(CH₂)_n-CH=N-NHC(=NH)NH₂
where $n = 1-10$

$R_2 = -NH_2$
-H
-OH
-O-CH₃
-O-R₃ where alkyloxy
group R₃ has 2-10
carbons including
hydrocarbon isomers
and/or hydroxylated
derivatives thereof
-aminoalkyl group
(1-10 carbons)
including hydrocarbon
isomers and/or
hydroxylated
derivatives thereof
-SO₂H
-CH₃
-(CH₂)_nCH₃ where n = 1-10
including hydrocarbon
isomers and/or
hydroxylated
derivatives thereof

$R' = -H$
-CH₃
-OH

$R'' = -H$
-CH₃
-OH

for controlling the symptoms of disorders selected from the group consisting of chronic gingivitis, chronic periodontitis, chronic autoimmune gastritis, ileitis, colitis, interstitial cystitis, arthritis, tendinitis, carpal tunnel syndrome and other cumulative trauma disorders, systemic lupus erythematosus, autoimmune vasculitis, asbestosis, silicosis, chronic obstructive pulmonary disease, Lyme disease, inflammatory myopathies, status epilepticus, inflammatory neuropathies, myasthenia gravis, multiple sclerosis, as well as lessening of inflammatory site edema, and treatment of post-event ischemia and reperfusion symptomatology resulting from acute central nervous system trauma, stroke and myocardial infarction.

In a preferred embodiment, the primary agent is used in a dosage in the range of one gram/day to 20 grams/day.

In a preferred embodiment, the primary agent is administered orally.

In a preferred embodiment, the primary agent is administered intravenously.

In a preferred embodiment, the co-agent is a non-absorbable polyamine substance or non-absorbable polyamine-related substance, a therapeutically effective amount of said co-agent acting to covalently bind to and sequester dietary carbonyl-containing products.

In a preferred embodiment, the co-agent is a non-absorbable polyamine substance or non-absorbable polyamine-related substance selected from the group consisting of:

- a. naturally occurring polysaccharides having beta-1,2, beta-1,3, beta-1,4 and/or beta-1,6 linkages containing aminosugars including the chitin class of biopolymers having the general structure of poly-beta-(1→4)-N-acetyl-D-glucosamine, and bearing at least one free primary amine group;
- b. deacetylated naturally occurring polysaccharides, having at least one N-acetylated residue, including chitosan, deacetylated chondroitin sulfate, or deacetylated hyaluronic acid;
- c. chemically aminated polysaccharides selected from the group consisting of:
aminodeoxy polysaccharides such as 2-amino-2-deoxy-cellulose;

aminoalkyl-, amino(hydroxyalkyl)-, aminoalkyl-ether-, and amino(hydroxyalkyl)-ether- derivatives of cellulose, chitin and other naturally occurring non-digestible carbohydrates selected from the group consisting of

$\text{H}_2\text{N}-(\text{CH}_2)_n-\text{[carbohydrate]}$ where $n = 1-10$, including alkyl isomers;

$\text{H}_2\text{N}-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $m = 0-10$ and $n = 0-10$;

$\text{H}_2\text{N}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$ where $n = 1-10$;

$\text{H}_2\text{N}-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$ where $m = 0-10$ and $n = 0-10$;

aminobenzyl- derivatives of cellulose, chitin or other naturally occurring non-digestible carbohydrates selected from the group consisting of

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{[carbohydrate]}$,

$\text{H}_2\text{N}-\text{CH}_2-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{[carbohydrate]}$,

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$ where $n = 0 - 10$, and

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$ where $m = 0-10$ and $n = 0-10$, including p-, o- and m-benzene ring amino-isomers, aminomethyl- isomers and alkyl group isomers thereof;

guanidine and aminoguanidine derivatives of cellulose, chitin or other naturally occurring non-absorbable carbohydrates selected from the group consisting of:

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{O}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{[carbohydrate]}$, where n = 1-10, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{O}-\text{[carbohydrate]}$, where n = 1-10, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{NH}-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{NH}-\text{(CH}_2\text{)}_n-\text{[carbohydrate]}$, where n = 1-10, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{NH}-\text{(CH}_2\text{)}_n-\text{O}-\text{[carbohydrate]}$, where n = 1-10, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{[carbohydrate]}$, where n = 1-10, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{O}-\text{[carbohydrate]}$, where n = 1-10, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{NH}-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{NH}-\text{(CH}_2\text{)}_n-\text{[carbohydrate]}$, where n = 1-10, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{NH}-\text{(CH}_2\text{)}_n-\text{O}-\text{[carbohydrate]}$, where n = 1-10, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{[carbohydrate]}$, where n = 1-10, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{O}-\text{[carbohydrate]}$, where n = 1-10, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

d. primary amine, aminoguanidine and guanidine derivatives of sucrose polyesters having one or more carbonyl trapping functional group per molecule wherein each carbonyl trapping functional group is in the omega-, omega-1 or other isomeric position within the fatty acyl chains, wherein each fatty acyl

chain may have from 3 to 26 carbons, from one to five nitrogen functional groups and from one to 24 hydroxyl groups;

c. synthetic polysaccharides consisting partly or entirely of aminosugars bound by beta-1,2, beta-1,3, beta-1,4 and/or beta-1,6 linkages;

f. mixed polysaccharide polymeric derivatives wherein primary amine, aminoalkyl (one to ten carbons per alkyl group), amino-hydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidinylalkyl (one to ten carbons per alkyl group), aminoalkyl-guanidinyl (one to ten carbons per alkyl group), guanidine, aminobenzene and/or aminoalkylbenzene (one to ten carbons per alkyl group) functional groups are covalently attached to matrices such as cpi-chlorohydrin copolymers of cellulose or chitin and wherein hydrocarbon spacer groups may include alkene as well as alkyl groups; and

g. non-polysaccharide polymeric derivatives wherein primary amine, aminoalkyl (one to ten carbons per alkyl group), amino-hydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidinylalkyl (one to ten carbons per alkyl group), aminoalkyl-guanidinyl (one to ten carbons per alkyl group), guanidine, aminobenzene and/or aminoalkylbenzene (one to ten carbons per alkyl group) functional groups are covalently attached to a synthetic non-digestible polymer selected from the group consisting of polystyrene, styrene-divinylbenzene copolymer, polyvinyl alcohol and crosslinked derivatives thereof, and wherein hydrocarbon spacer groups may include alkene as well as alkyl groups,

for controlling the symptoms of disorders selected from the group consisting of chronic gingivitis, chronic periodontitis, chronic autoimmune gastritis, ileitis, colitis, interstitial cystitis, arthritis, tendinitis, carpal tunnel syndrome and other cumulative trauma disorders, systemic lupus erythematosus, autoimmune vasculitis, asbestosis, silicosis, chronic obstructive pulmonary disease, Lyme disease, inflammatory myopathies, status epilepticus, inflammatory neuropathies, myasthenia gravis, multiple sclerosis, as well as lessening of inflammatory

site edema, and treatment of post-event ischemia and reperfusion symptomology resulting from acute central nervous system trauma, stroke and myocardial infarction.

In a preferred embodiment, the co-agent is a non-absorbable polyamine substance or non-absorbable polyamine-related substance which is in a microfibrillated form or microcrystalline form having enhanced surface area, increased porosity, increased water retention capacity and enhanced chemical accessibility.

In a preferred embodiment, the therapeutically effective amount of said co-agent is a dosage in the range of one gram/day to 40 grams/day.

In a preferred embodiment, the therapeutically effective amount of said non-absorbable polyamine co-agent or non-absorbable polyamine-related co-agent is administered orally.

In another preferred embodiment, the use additionally comprises use of at least one co-agent selected from the group consisting of antioxidants and free radical trapping compounds, chemicals having indirect antioxidant properties, suspending reagents, vitamins and derivatives thereof, chemical conjugating agents which facilitate kidney drug elimination, metabolites at risk of depletion, and sulphydryl containing chemicals,

for controlling the symptoms of disorders selected from the group consisting of chronic gingivitis, chronic periodontitis, chronic autoimmune gastritis, ileitis, colitis, interstitial cystitis, arthritis, tendinitis, carpal tunnel syndrome and other cumulative trauma disorders, systemic lupus erythematosus, autoimmune vasculitis, asbestosis, silicosis, chronic obstructive pulmonary disease, Lyme disease, inflammatory myopathies, status epilepticus, inflammatory neuropathies, myasthenia gravis, multiple sclerosis, as well as lessening of inflammatory site edema, and treatment of post-event ischemia and reperfusion symptomology resulting from acute central nervous system trauma, stroke and myocardial infarction.

In another preferred embodiment, one or more co-agent selected from the group consisting of antioxidants and free radical trapping compounds, chemicals having indirect antioxidant properties, suspending reagents, vitamins and derivatives thereof, chemical conjugating agents which facilitate kidney

drug elimination, metabolites at risk of depletion, and sulfhydryl containing chemicals is administered orally.

In another preferred embodiment, one or more co-agent selected from the group consisting of antioxidants and free radical trapping compounds, chemicals having indirect antioxidant properties, suspending reagents, vitamins and derivatives thereof, chemical conjugating agents which facilitate kidney drug elimination, metabolites at risk of depletion, and sulfhydryl containing chemicals is administered intravenously.

In another aspect of this invention, the invention relates to the use of a composition for treating a mammal suffering from a chronic inflammatory disorder featuring pathology which includes in part increased lipid peroxidation comprising orally or intravenously administering a therapeutically effective amount of a primary agent in combination with at least one co-agent, wherein said mammalian disorder is selected from a group consisting of arthritis, inflammatory site edema, acute central nervous system trauma, stroke and myocardial infarction, wherein the primary therapeutic agent is selected from the group consisting of primary amine and amine-related benzoic acid derivatives which are water soluble and of molecular weight 100 to 1,400 as defined above, wherein the primary agent acts by covalently binding to and sequestering carbonyl compounds in said mammal which result from increased lipid peroxidation, and wherein said primary agent is administered with at least one co-agent selected from the group consisting of non-absorbable polyamine substances, non-absorbable polyamine-related substances, antioxidants and free radical trapping compounds, chemicals having indirect antioxidant properties, suspending reagents, vitamins and derivatives thereof, chemical conjugating agents which facilitate kidney drug elimination, metabolites at risk of depletion, and sulfhydryl containing chemicals as defined above.

In a preferred embodiment, the primary agent of this invention is used to treat a mammal in a dosage in the range of 10 mg/kg/day to 1.0 gm/kg/day.

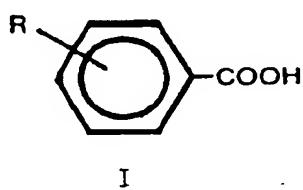
In a preferred embodiment, the non-absorbable polyamine substance or non-absorbable polyamine-related substance as

defined above is used to treat a mammal in a dosage in the range of 10 mg/kg/day to 1.0 gm/kg/day.

In another aspect of the invention, the invention relates to a pharmaceutical composition for use in the treatment of the symptoms of disorders selected from the group consisting of:

chronic gingivitis, chronic periodontitis, chronic autoimmune gastritis, ileitis, colitis, interstitial cystitis, arthritis, tendinitis, carpal tunnel syndrome and other cumulative trauma disorders, systemic lupus erythematosus, autoimmune vasculitis, asbestosis, silicosis, chronic obstructive pulmonary disease, Lyme disease, inflammatory myopathies, status epilepticus, inflammatory neuropathies, myasthenia gravis, multiple sclerosis, as well as lessening of inflammatory site edema, and treatment of post-event ischemia and reperfusion symptomology resulting from acute central nervous system trauma, stroke and myocardial infarction,

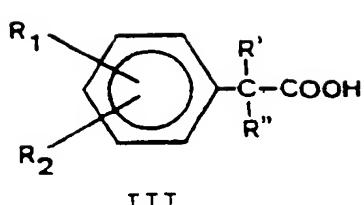
the composition comprising one or more water soluble, low molecular weight primary agent (100 to 1,400 range of molecular weights) selected from the free acid forms, salts, benzene ring isomers, amide derivatives, carboxylic acid ester derivatives and analogous non-aromatic benzene ring derivatives of the group consisting of:



R = -NH₂,
 -aminoalkyl group having 1-10 carbons including hydrocarbon isomers and/or hydroxylated derivatives thereof
 -NHC(=NH)NH₂,
 -(CH₂)_nNHC(=NH)NH₂, where n = 1-10
 -C(=NH)-NH₂,
 -(CH₂)_n-CH=NC(=NH)NH₂, where n = 1-10
 -NHC(=NH)NNNH₂,
 -(CH₂)_nNHC(=NH)NNNH₂, where n = 1-10
 -(CH₂)_n-CH=NC(=NH)NNNH₂, where n = 1-10
 -NNHNC(=NH)NH₂,
 -(CH₂)_n-NNHNC(=NH)NH₂, where n = 1-10
 -(CH₂)_n-CH=N-NHC(=NH)NH₂, where n = 1-10

$R_1 = -NH_2$
 -aminoalkyl group
 (1-10 carbons)
 including hydrocarbon
 isomers and/or
 hydroxylated
 derivatives thereof
 $-(CH_2)_nNHC(=NH)NH_2$
 where $n = 1-10$
 $-C(=NH)-NH_2$,
 $-(CH_2)_n-CH=NC(=NH)NH_2$
 where $n = 1-10$
 $-NHC(=NH)NHNH_2$,
 $-(CH_2)_nNHC(=NH)NHNH_2$,
 where $n = 1-10$
 $-(CH_2)_n-CH=NC(=NH)NHNH_2$,
 where $n = 1-10$
 $-NHNHC(=NH)NH_2$,
 $-(CH_2)_n-NHNHC(=NH)NH_2$,
 where $n = 1-10$
 $-(CH_2)_n-CH=N-NHC(=NH)NH_2$,
 where $n = 1-10$

$R_2 = -NH_2$,
 $-OH$,
 $-O-CH_3$,
 $-O-R'$ with alkyloxy
 group R' having 2-10
 carbons including
 hydrocarbon isomers
 and/or hydroxylated
 derivatives thereof
 -aminoalkyl group
 (1-10 carbons)
 including hydrocarbon
 isomers and/or
 hydroxylated
 derivatives thereof
 $-SO_3H$,
 $-CH_3$,
 $-(CH_2)_nCH_3$ where $n = 1-10$
 including hydrocarbon
 isomers and/or
 hydroxylated
 derivatives thereof



$R_1 = -(CH_2)_n-NH_2$ where $n = 0-10$
 including isomers of
 the aminoalkyl group
 and hydroxylated
 derivatives thereof
 $-C(=NH)-NH_2$,
 $-NHC(=NH)NH_2$,
 $-(CH_2)_nNHC(=NH)NH_2$,
 where $n = 1-10$
 (continued)

$-(CH_2)_n-CH=NC(=NH)NH_2$,
 where $n = 1-10$
 $-NHC(=NH)NHNH_2$,
 $-(CH_2)_nNHC(=NH)NHNH_2$,
 where $n = 1-10$
 $-(CH_2)_n-CH=NC(=NH)NHNH_2$,
 where $n = 1-10$
 $-NHNHC(=NH)NH_2$,
 $-(CH_2)_n-NHNHC(=NH)NH_2$,
 where $n = 1-10$
 $-(CH_2)_n-CH=N-NHC(=NH)NH_2$,
 where $n = 1-10$

$R_2 = -NH_2$
 $-H$
 $-OH$
 $-O-CH_3$
 $-O-R_3$, where alkyloxy group R_3 has 2-10 carbons including hydrocarbon isomers and/or hydroxylated derivatives thereof
 -aminoalkyl group (1-10 carbons) including hydrocarbon isomers and/or hydroxylated derivatives thereof
 $-SO_3H$
 $-CH_3$
 $-(CH_2)_nCH_3$, where $n = 1-10$ including hydrocarbon isomers and/or hydroxylated derivatives thereof

$R' = -H$
 $-CH_3$
 $-OH$

$R'' = -H$
 $-CH_3$
 $-OH$

in a dosage range of from one gram/day to 20 grams/day, in association with a pharmaceutically acceptable carrier thereof.

In another preferred embodiment, this pharmaceutical composition comprises the use of at least one co-agent.

In another aspect of this invention, the invention relates to a pharmaceutical composition for use in the treatment of the symptoms of disorders selected from the group consisting of:

chronic gingivitis, chronic periodontitis, chronic autoimmune gastritis, ileitis, colitis, interstitial cystitis, arthritis, tendinitis, carpal tunnel syndrome and other

cumulative trauma disorders, systemic lupus erythematosus, autoimmune vasculitis, asbestosis, silicosis, chronic obstructive pulmonary disease, Lyme disease, inflammatory myopathies, status epilepticus, inflammatory neuropathies, myasthenia gravis, multiple sclerosis, as well as lessening of inflammatory site edema, and treatment of post-event ischemia and reperfusion symptomology resulting from acute central nervous system trauma, stroke and myocardial infarction.

the composition comprising one or more non-absorbable polyamine co-agent or non-absorbable polyamine-related co-agent selected from the group consisting of:

- a. naturally occurring polysaccharides having beta-1,2, beta-1,3, beta-1,4 and/or beta-1,6 linkages containing aminosugars including the chitin class of biopolymers having the general structure of **poly-beta-(1→4)-N-acetyl-D-glucosamine**, and bearing at least one free primary amine group;
- b. deacetylated naturally occurring polysaccharides, having at least one N-acetylated residue, including chitosan, deacetylated chondroitin sulfate, or deacetylated hyaluronic acid;
- c. chemically aminated polysaccharides selected from the group consisting of:

aminodoxy polysaccharides such as 2-amino-2-deoxy-cellulose;

aminoalkyl-, amino(hydroxyalkyl)-, aminoalkyl-ether-, and amino(hydroxyalkyl)-ether- derivatives of cellulose, chitin and other naturally occurring non-digestible carbohydrates selected from the group consisting of

$\text{H}_2\text{N}-(\text{CH}_2)_n-\text{[carbohydrate]}$ where $n = 1-10$, including alkyl isomers;

$\text{H}_2\text{N}-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $m = 0-10$ and $n = 0-10$;

$\text{H}_2\text{N}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$ where $n = 1-10$;

$\text{H}_2\text{N}-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$ where $m = 0-10$ and $n = 0-10$;

aminobenzyl- derivatives of cellulose, chitin or other naturally occurring non-digestible carbohydrates selected from the group consisting of

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{[carbohydrate]}$,

$\text{H}_2\text{N}-\text{CH}_2-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{[carbohydrate]}$,

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$ where $n = 0 - 10$, and

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$ where $m = 0-10$ and $n = 0-10$, including p-, o- and m-benzene ring amino-isomers, aminomethyl- isomers and alkyl group isomers thereof;

guanidine and aminoguanidine derivatives of cellulose, chitin or other naturally occurring non-absorbable carbohydrates selected from the group consisting of:

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{O}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{N}=\text{CH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{N}=\text{CH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{NH}-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{N}=\text{CH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$,

including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{O}-[\text{carbohydrate}]$, where n = 1-10, including hydrocarbon isomers, other linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{NH}-[\text{carbohydrate}]$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{NH}-\text{(CH}_2\text{)}_n-[\text{carbohydrate}]$, where n = 1-10, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{NH}-\text{(CH}_2\text{)}_n-\text{O}-[\text{carbohydrate}]$, where n = 1-10, including hydrocarbon isomers, other linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-[\text{carbohydrate}]$, where n = 1-10, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{O}-[\text{carbohydrate}]$, where n = 1-10, including hydrocarbon isomers, other linkage isomers and hydroxylated derivatives thereof;

d. primary amine, aminoguanidine and guanidine derivatives of sucrose polyesters having one or more carbonyl trapping functional group per molecule wherein each carbonyl trapping functional group is in the omega-, omega-1 or other isomeric position within the fatty acyl chains, wherein each fatty acyl chain may have from 3 to 26 carbons, from one to five nitrogen functional groups and from one to 24 hydroxyl groups;

e. synthetic polysaccharides consisting partly or entirely of aminosugars bound by beta-1,2, beta-1,3, beta-1,4 and/or beta-1,6 linkages;

f. mixed polysaccharide polymeric derivatives wherein primary amine, aminoalkyl (one to ten carbons per alkyl group), amino-hydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidylalkyl (one to ten carbons per alkyl group), aminoalkyl-guanidinyl (one to ten carbons per alkyl group), guanidine, aminobenzene and/or aminoalkylbenzene (one to ten carbons per alkyl group) functional groups are covalently attached to matrices such as 2,3,6-tri-O-chlorohydrin copolymers of cellulose or

chitin and wherein hydrocarbon spacer groups may include alkene as well as alkyl groups; and

g. non-polysaccharide polymeric derivatives wherein primary amine, aminoalkyl (one to ten carbons per alkyl group), aminohydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidinylalkyl (one to ten carbons per alkyl group), aminoalkylguanidinyl (one to ten carbons per alkyl group), guanidine, aminobenzene and/or aminoalkylbenzene (one to ten carbons per alkyl group) functional groups are covalently attached to a synthetic non-digestible polymer selected from the group consisting of polystyrene, styrene-divinylbenzene copolymer, polyvinyl alcohol and crosslinked derivatives thereto, and wherein hydrocarbon spacer groups may include alkene as well as alkyl groups,

in a dosage range of from one gram/day to 40 grams/day, in a microfibrillated form or microcrystalline form having enhanced surface area, increased porosity, increased water retention capacity and enhanced chemical accessibility, and in association with a pharmaceutically acceptable carrier thereto.

In another aspect of this invention, the invention relates to a pharmaceutical composition comprising at least one co-agent selected from the group consisting of antioxidants and free radical trapping compounds, chemicals having indirect antioxidant properties, suspending reagents, vitamins, chemical conjugating agents which facilitate kidney drug elimination, metabolites at risk of depletion, and sulfhydryl containing chemicals.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the clinical treatment of chronic inflammatory diseases, including chronic gingivitis, chronic periodontitis, chronic autoimmune gastritis, ileitis, colitis, interstitial cystitis, arthritis, tendinitis, carpal tunnel syndrome and other cumulative trauma disorders, systemic lupus

erythematosus, autoimmune vasculitis, asbestosis, silicosis, chronic obstructive pulmonary disease, Lyme disease, inflammatory myopathies, status epilepticus, inflammatory neuropathies, myasthenia gravis, multiple sclerosis, as well as lessening of inflammatory site edema, and treatment of post-event ischemia and reperfusion symptomology resulting from acute central nervous system trauma, stroke and myocardial infarction. No pharmacological treatment of comprehensive effectiveness is currently available for any of the chronic inflammatory disorders or etiologically related symptomology discussed herein.

2. Description of Prior Art

The logic and potential value, even synergistic value, of using two or more therapeutic agents in combination has been recognized previously (Ghose and coworkers, 1983; Flood and coworkers, 1988; Goldstein and coworkers, 1990, pg. 102; Rinne, 1991). For example, Brooks and Schwarzer (1991) noted that:

Long term (five years or more) studies of SAARDs [slow acting antirheumatic drugs] in rheumatoid arthritis suggest that less than 50% of patients are taking gold, D-penicillamine, sulphasalazine, or anti-malarial drugs five years after the start.¹¹⁻¹⁵ Patients whose disease was initially controlled by these agents ceased taking the drugs because of either the development of side effects or a flare in disease activity, despite continuation of the treatment...

...As the pathogenetic processes of rheumatoid arthritis are so complex it is extremely unlikely that any single agent will block all the pathways leading to joint destruction. It might, therefore, be reasonable to consider using combinations of drugs, either simultaneously or cyclically...

Numerous prior art publications disclose that vitamin E functions physiologically as a lipid-soluble antioxidant free radical trapping agent. Prior art publications describe

methionine as a water-soluble agent, an essential amino acid, an antioxidant and a free radical trapping agent.

Primary agents of this invention are selected from the group consisting of p-aminobenzoic acid (PABA) and derivatives thereof. p-Aminobenzoic acid is known as a water-soluble B vitamin, and several published studies have presented evidence to the effect that PABA functions, in part, as a weak antioxidant and a weak free radical trapping agent (Maksimov and Rcbachuk, 1985, Table 2; Pryor and coworkers, 1976, pg. 201).

In so far as benzoic acid or derivatives thereof have been recognized as antioxidants or free radical trapping agents, their mechanism of action is understood to consist of hydroxyl radical trapping by the benzene ring (Grootveld and Halliwell, 1988; Halliwell and Gutteridge, 1985, pp. 105 and 130; Richmond and coworkers, 1981; Rcpine and coworkers, 1979, pg. 1642). This has been explicitly demonstrated for PABA (Nakken, 1964, pp. 446, 448, 454-457; Nakken and Pihl, 1966, pp. 21, 22, 24, 25 and 28). Likewise, mannitol is recognized as an antioxidant based on its ability to scavenge hydroxyl radicals (Halliwell and Gutteridge, 1985, pp. 97 and 105), and a similar mechanism of action is recognized for dimethyl sulfoxide (Halliwell and Gutteridge, 1985, pg. 147) and methionine (Del Maestro, 1980, 164-165).

Clinical use of the drug sulfasalazine (SAZ) represents a well documented example of the use of a benzoic acid derivative as a trapping agent for the hydroxyl radical and other free radicals in the treatment of a chronic inflammatory disease. In the colon SAZ undergoes reductive cleavage to liberate 5-amino-salicylic acid (5-ASA), which is the therapeutically active agent. Ahnfelt-Ronen and coworkers (1990) have presented research findings which document the use of sulfasalazine for successful treatment of chronic inflammatory bowel disease (CIBD), also known as ulcerative colitis. Summarizing their work, these investigators noted:

The present results thus lead us to propose the following mechanism of action of SAZ in the treatment of CIBD. After cleavage of SAZ by reductive processes in the colon, 5-ASA is released in high concentrations. 5-Aminosalicylic acid is a highly effective scavenger of free radicals and interacts with hydroxyl and other radicals to form a novel major metabolite of 5-ASA, M1 and several minor metabolites. In this reaction, 5-ASA breaks the free radical chain reaction. The cytotoxic and tissue-destructive effects of this otherwise perpetuating process are thereby gradually aborted. This action of 5-ASA manifests itself clinically as an antiinflammatory effect, and the proposed mechanism of action implies that free radicals are of major importance in producing the clinical signs of chronic inflammation... (pgs. 1168-1169)

Yet several points serve to distinguish this previous work on SAZ from the present invention. Based on high performance liquid chromatographic elution times and ultraviolet spectra data, Ahnfelt-Ronne compared their in vivo 5-ASA metabolic products to products observed after in vitro hydroxylation of 5-ASA by the Fenton reaction and tentatively identified 5-ASA metabolites as being hydroxylated derivatives. Yet they never explicitly identified the chemical structures of the disease-specific metabolic products they observed. Nor was there any attempt on their part to look for evidence of in vivo trapping of carbonyl products. Dull and coworkers (1987, pg. 2469) used mass spectrometry to definitively identify two of the several hydroxylation/oxidative deamination products which result from in vitro incubation of 5-ASA with activated human mononuclear cells. They identified these products as gentisic acid (2,5-dihydroxybenzoic acid) and salicylic acid (2-hydroxy benzoic acid), while five other 5-ASA metabolic products remained unidentified (pg. 2470).

There also was a curious methodological oversight in the study

of Ahnfelt-Ronne and coworkers. They included several rheumatoid arthritis (RA) patients in their SAZ study as one of their control groups and reported, in part:

...The presence of M1 and other Fenton reaction products of 5-ASA in extracts of feces samples from CIBD patients treated with SAZ is clearly demonstrated.

In contrast, none of the metabolites M1-M6 were detected in stool extracts from SAZ-treated RA patients. These extracts contained 5-ASA, sulfapyridine, and N-acetyl-5-ASA in the normal range for SAZ-treated patients... (pg. 1165)

This represents a misconceived use of a control group, as CIBD is a chronic inflammatory disorder of the intestinal tract, while RA is not. Ahnfelt-Ronne and coworkers failed to examine urine or blood samples from their RA patients for evidence of metabolites M1-M6, which is where one would logically expect to find such metabolites.

Ahnfelt-Ronne and colleagues, like earlier investigators, never recognized the possibility of using a therapeutic agent to scavenge carbonyl products of inflammation. Hence they never recognized the possibility of intentionally using a composition consisting of a primary agent which sequesters carbonyl products in combination with co-agents that have known antioxidant properties.

Further distinctions should be noted between the present invention and previously recognized clinical use of SAZ in that SAZ releases sulfapyridine, a somewhat toxic substance, into the body (Peppercorn, 1984, pgs. 377-379 and 383), while the present invention does not, and use of sulfasalazine depends on intestinal bacteria for activation of the drug, while the primary agents of the present invention do not. Besides use in treatment of CIBD and ileitis (Budavari and coworkers, 1989, pg. 1412), SAZ has been recognized, at least at the experimental

level, for treatment of radiation bowel disease, scleroderma, dermatitis herpetiformis and rheumatoid arthritis (Peppercorn, 1984, pgs 380-381).

Other examples of amine drugs recognized as having anti-inflammatory properties include para-substituted N-benzenesulfonyl derivatives of anthriliic acid (Borne and coworkers, 1974), 4-amino benzoic acid anilides (Thiele, 1971; Deutsche Gold- und Silber-Scheideanstalt vorm. Roessler, 1972) and Tinoridine (Shimada and Yasuda, 1979). The chemical structures of these agents lie beyond the present invention, they are not presently recognized as carbonyl sequestering agents, and they have not been used in multiple ingredient compositions analogous to those of the present invention.

Several drug products containing PABA have been marketed for human use in the United States. However, none include the inventive concept or compositions claimed herein. Potassium p-aminobenzoate has been marketed as Potaba (R) in the pure form as an antifibrotic, i.e., skin softening, agent (Drug Information for the Health Care Professional, 8th ed., 1988, pgs. 111-113). As such it has been recognized for treatment of Peyronie's disease; diffuse systemic sclerosis; morphea and linear scleroderma; and dermatomyositis. For such purposes, Potaba (R) is taken orally in average doses of 12 grams/day for up to two years, although human use of 15 - 20 grams/day is recognized. As an ingredient in analgesic tablets, PABA has been marketed for domestic human use (300 mg/tablet) in Pabirin (R) buffered tablets (with aspirin), in Pabolate (R) tablets (with sodium salicylate) and in Pabolate-SF (R) tablets (with potassium salicylate), as described in Physicians' Desk Reference (Huff, 1980, pgs. 849, with aspirin and 1430, with salicylates). Five percent PABA in a cream base has also been marketed as a sunscreen product (Physicians' Desk Reference, Huff, 1980, pg. 849).

In its summary on systemic use of PABA the Drug Information for the Health Care Professional text (8th ed., 1988, pg. 111)

presented the following statement (reproduced herein its entirety):

Mechanism of action: The mechanism by which aminobenzoate potassium exerts its antifibrotic effect is not known. It has been postulated that fibrosis results from an imbalance of serotonin and monoamine oxidase (MAO) mechanisms at the tissue level. Fibrosis is believed to occur when an excessive serotonin effect is sustained over a period of time. This could be the result of too much serotonin or too little MAO activity. Aminobenzoate potassium increases oxygen utilization at the tissue level. It has been suggested that this increased oxygen utilization could enhance the degradation of serotonin by enhancing MAO activity or other activities that decrease the tissue concentration of serotonin.

In its summary on systemic use of potassium p-aminobenzoate the Physician's Desk Reference (Dowd, 1993, pg. 1103) presented the following statement (reproduced herein its entirety):

INDICATIONS

Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

'Possibly' effective: Potassium aminobenzoate is possibly effective in the treatment of scleroderma, dermatomyositis, morphea, linear scleroderma, pemphigus, and Peyronie's disease.

Final classification of the less-than-effective indications requires further investigation.

ADVANTAGES

POTABA offers a means of treatment of serious and often chronic entities involving fibrosis and nonsuppurative inflammation.

PHARMACOLOGY

P-Aminobenzoate is considered a member of the vitamin

B complex. Small amounts are found in cereal, eggs, milk and meats. Detectable amounts are normally present in human blood, spinal fluid, urine, and sweat. PABA is a component of several biologically important systems, and it participates in a number of fundamental biological processes. It has been suggested that the antifibrosis action of POTABA is due to its mediation of increased oxygen uptake at the tissue level. Fibrosis is believed to occur from either too much serotonin or too little monoamine oxidase activity over a period of time. Monoamine oxidase requires an adequate supply of oxygen to function properly. By increasing oxygen supply at the tissue level POTABA may enhance MAO activity and prevent or bring about regression of fibrosis.

This inventor sees no relationship of such comments to the present invention. In particular, the comments noted above clearly do not recognize the potential use of PABA and derivatives thereof as carbonyl trapping agents, that is, as agents which may generally inhibit chronic inflammatory disorders by virtue of their ability to chemically bind to and sequester aldehyde and ketone products of lipid peroxidation which result from and contribute to the continuation of chronic inflammatory disorders. Hence the clinical applications of PABA and derivatives thereof claimed in the present invention are regarded by the inventor as new and novel.

Certain amino agents have recognized antioxidant properties. These include N,N'-di-(sec-butyl)-p-phenylenediamine (Scott, 1965, pg. 120), aniline and aniline N-substituted agents (Scott, 1965, pg. 125). In the present invention focus is placed on primary amine agents, as such agents are known to covalently react with carbonyl agents to yield Schiff base-type products (Fecney and coworkers, 1975, pg. 141). By contrast, N-substitution with hydrocarbon functional groups tends to increase amine antioxidant activity (Scott, 1965, pgs. 125 and 148). These are two distinct chemical phenomena. The antioxidant

property of amines depends on their ability to act as electron donors to alkoxy or alkylperoxy radicals (Scott, 1965; pgs. 127, 145 and 158). The carbonyl trapping property of amines depends on their ability to form Schiff base-type addition products.

Vitamin C (ascorbic acid) is widely recognized as a water-soluble antioxidant vitamin. However, numerous published studies which have appeared since 1980 document that vitamin C also can act physiologically as a pro-oxidant (Gutteridge and Wilkins, 1982), an agent which stimulates lipid peroxidation (Chojkier and coworkers, 1989, pgs. 16957 and 16961), and that it is a strong protein glycosylating agent (Ortwerth and Olcsen, 1988, pgs. 12, 14, 16, 18 and 20). Thus, for example, in vitro studies have documented the ability of vitamin C to accelerate the process of cataract formation (Slight and coworkers, 1990, pgs. 369-373). In addition, some evidence suggests that ascorbic acid may act as a factor which stimulates certain reactions which are characteristic of inflammatory diseases. For example, the presence of ascorbic acid in the synovial fluid of the arthritic joint may contribute to degradation of hyaluronic acid (Wong and coworkers, 1981; Higson and coworkers, 1988).

The use of vitamin B₆ as a primary agent in combination with co-agents such as vitamins C, E, A, B₁, B₅, as well as dimethyl sulfoxide, PABA, inositol, selenium, butylated hydroxytoluene, thiadipropionates, choline, cysteine, zinc and D-penicillamine has been described for clinical treatment of arthritis, together with use of a water bed (Pearson and Shaw, 1982, pp. 298-300). Numerous other variations on this list of co-agents have been described publicly (see Passwater, 1985).

The disclosure of Pearson and Shaw contains several deficiencies which are resolved by the present invention. They did not recognize the pro-oxidant, the lipid peroxidation stimulating or the protein glycosylating properties of vitamin C. Noting these deleterious properties of vitamin C, this inventor regards excess vitamin C consumption (beyond the RDA, 60 mg/day) to be a risk factor for exacerbating the physiological and clinical

effects of arthritis and other chronic inflammatory diseases. In contrast, Pearson and Shaw (1982) refer repeatedly to vitamin C as the primary agent of their many compositions (for example, pgs. 468-469 and 611-613).

Nor did Pearson and Shaw recognize the ability of aldehydic trapping agents such as PABA to chemically react with and sequester aldehydes which may result from and contribute to the inflammatory cascade process. This inventive oversight on their part is of fundamental importance. This explains why Pearson and Shaw listed PABA only as one of many "anti-oxidant" and "membrane stabilizer" co-agents. In contrast, PABA and derivatives thereof are identified as the class of primary agents in the present invention.

At least two other deficiencies of the Pearson and Shaw prior art disclosure are addressed by the present invention. D-Penicillamine has been recognized as an anti-arthritis drug based on its abilities to inhibit lipid peroxidation by neutralization of free radicals and to bind iron or copper ions (Kostyuk and coworkers, 1990, pg. 39; Demopoulos, 1973, pgs. 1904 and 1906). D-Penicillamine has known predictable long term toxic properties which severely limit its practical use on humans (Demopoulos, 1973, pg. 1906; Zuckerman and coworkers, 1980, pg. 430). Its toxic properties prevent its use on a long term, on-going basis, as required for the clinical treatment of the disorders addressed herein. In addition, L-cysteine has been recognized as a neurotoxic agent when used under certain laboratory circumstances (Olney and coworkers, 1990). As Olney and coworkers stated, "after systemic administration to immature rodents, L-cysteine destroys neurons in the cerebral cortex, hippocampus, thalamus, and striatum..." (pg. 596). Hence use of cysteine is also deleted from the present invention.

Zarafonetis (1953) has reported some success in treatment of rheumatoid arthritis by use of potassium p-aminobenzoate in combination with acetylsalicylic acid and cortisone. In this report Zarafonetis also described some success in clinical

treatment of dermatomyositis and scleroderma by use of potassium p-aminobenzoate alone, and referred to earlier work on these disorders and other clinically related syndromes, including forms of lupus erythematosus.

Yet Zarafontis based his logic for diversifying clinical studies on PABA or its potassium salt solely on similarities of clinical symptoms, comparisons among clinical syndromes which feature some common symptomology (Zarafontis, 1953, pp 667-668; Zarafontis, 1964, pgs. 550 and 560; Priceley and Brown, 1979, pg. 161; Zarafontis and coworkers, 1988, pg. 194). Zarafontis never stated an understanding or recognized that PABA has the physiological potential of serving as an aldehyde chemical trapping agent (Zarafontis, 1953, pg. 671). Hence, he never recognized its potential to sequester aldehyde products resulting from increased lipid peroxidation secondary to site-specific inflammation. In failing to recognize this principle, Zarafontis failed to recognize the potential full scope of clinical applications of PABA. Failing to recognize the potential of synergistic antioxidant co-agents, the procedures of Zarafontis for treatment of scleroderma, rheumatoid arthritis and dermatomyositis relied on use of high PABA dosages (12-18 gm/day; see Zarafontis, 1953, pg. 666). In principle, it is the understanding of this inventor that the clinical prognosis of any disease which features increased lipid peroxidation as part of its etiology may be improved by clinical application of the present inventive concept.

Zarafontis (1953) also referred to an earlier study which used a combination of p-aminobenzoic acid and alpha-tocopherol to treat scleroderma. Gougerot and Hewitt (1951) described the logic of their scleroderma treatment protocol as follows:

This observation is to be added to the file of the treatment of scleroderma. Zarafontis and his collaborators have already published 5 cases of scleroderma improved by para-aminobenzoic acid, and in the same therapeutic series

Shaffer and his collaborators treated a generalized scleroderma with para-aminobenzoic acid with improvement. In a study of a completely different nature, vitamin E (α -tocopherol) was used by Klempner, etc. and in France by Baze (Lyon, July 1949). This is why we have associated the two therapies because of their effect on diseases of collagen.

As such, they perceived their clinical treatment strategy to address the status of collagen, with no discussion of possible physiological mechanisms. Compared to the present invention, Gougerot and Hewitt:

- (1) failed to recognize that either of their therapeutic agents may interfere with the inflammatory cascade,
- (2) failed to recognize that primary amine and amine-related derivatives of benzoic acid, as a class, may bind to and sequester aldehydes which result from the inflammatory process, and
- (3) failed to understand that the combination of a water soluble aldehyde-trapping primary amine agent and a lipophilic antioxidant agent may have clinical application to the treatment of a broad spectrum of chronic inflammatory diseases.

One additional clinical study based on use of PABA falls within the scope of prior art regarding the present invention. In 1967 McL'nikova and Ryzhova presented the results of a clinical trial wherein PABA was used to treat post-event trauma in experimental myocardial infarction, as studied in rabbits and dogs. Myocardial infarction was induced by silk ligature of the left coronary artery and vein. McL'nikova and Ryzhova reported, in part:

One of the more important problems facing modern pharmacology is the search for substances capable

of restoring the circulation of the heart in myocardial infarction. Improvement in the coronary circulation may be obtained both by a direct coronary-dilator effect on the vessels of the heart and by influences acting on metabolic processes and the hemodynamics in the heart muscle. From this point of view there is considerable interest in procaine and the product of its hydrolysis - p-aminobenzoic acid (PABA), an active component of procaine, taking part in intimate biochemical processes and possessing a well-defined antihistamine action... (pg. 389)

The animals of series II (25 rabbits and 5 dogs) with an acute myocardial infarct received subcutaneous injections of PABA in doses of 12-15 mg/kg daily, twice a day throughout the period of observation. Examination of the electrocardiographic, clinical, and laboratory findings for the rabbits and dogs treated with PABA (12 mg/kg) on the second day showed restoration of the normal rhythm with disappearance of the extrasystoles, an increase in the voltage of the waves, and some reduction in the depth of the QS waves, evidently as a result of improvement of the coronary circulation... On the 9th-14th day, in 85% of the animals (receiving 12 mg/kg PABA) the ECG and results of the clinical and laboratory investigations were normal, while in the remaining 15% of animals, organization of the myocardial infarct took place on the 16th-18th day... (pg. 390)

Special attention was drawn to the well marked vascularization both in the areas of connective scar tissue and throughout the myocardium, mainly as a result of dilatation of the capillaries and an increase in the number of arteries, and also to the absence of necrosis in the perifocal zone.

In acute experiments on cats (by N. V. Kaverina's method) a constant and well marked coronary-dilator effect was observed in response to injection of PABA

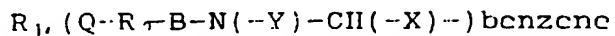
(15-20 mg/kg), as shown by a considerable increase in the volume velocity of the coronary blood flow (by 80-108%) and also by a distinct reduction in the oxygen consumption of the heart... (pg. 391)

As such, McL'nikova and Ryzhova have reported a coronary vasodilator effect of PABA based on their understanding of the drug's antihistamine property. They recognized no anti-inflammatory property of PABA and did not understand their findings within such a context. Subsequent work by Kурдин (1978) has presented evidence of increased lipid peroxidation in the process of myocardial infarction. Viewing both of these studies within the context of the present invention, the inventor proposes that, to some degree, the beneficial effects of PABA in the McL'nikova and Ryzhova study reflected an anti-inflammatory property of PABA unrecognized by the investigators, and that such a beneficial effect may be optimized by use of the multi-component compositions of the present invention. As defined below, the present invention is believed to have significant clinical value in the post-event treatment of myocardial infarction, acute central nervous system trauma and stroke.

United States Patent No. 5,002,703 (Warner-Lambert Co.) is entitled "Benzoinic acid and benzoinic acid ester derivatives having antiinflammatory and analgesic activity." Its utility is described as applying to "...treatment of arthritis, asthma, Raynaud's disease, inflammatory bowel disorders, trigeminal or herpetic neuralgia, inflammatory eye disorders, psoriasis, dental pain, and headaches, particularly vascular headache, such as migraine, cluster, mixed vascular syndromes, as well as nonvascular, tension headaches." The mechanism of action as defined in this patent is different from the inventive concept of the present invention, the primary agents of the Warner-Lambert procedures are substantially different from those of the present invention, and the Warner-Lambert procedures do not involve multiple-ingredient compositions analogous to those of the present invention. All Warner-Lambert US patents of the series represented by US Patent 5,002,703 are based on claims regarding

compounds which are, by comparison to the present invention, relatively large, complex chemical derivatives of benzoic acid. For example, the primary agents of US Patent 5,002,703 are described as:

A compound of the formula



wherein: (a) R_1 is $COOR'$ wherein R' is H or lower alkyl of one to four carbons, inclusive; (b) B is $-SO_2-$; (c) X and Y are independently H or lower alkyl of one to four carbons, inclusive; (d) R_2 is alkylene, alkenylene, alkynylene branched or linear chains of 1 to 11 carbons, inclusive; (e) Q is $COOH$, Br , NH_2 , cyclohexyl, or 2-naphthyl-0-; ~~or~~ or nontoxic, pharmaceutically acceptable acid addition or base salt thereof.

Chemical structures of this kind clearly lie beyond the claims of the present invention.

Broad spectrum clinical use of anti-inflammatory vitamin compositions which feature PABA as a primary agent, and the methodological reasoning for doing so, has not been previously recognized or described. p-Aminobenzoic acid is not presently recognized as a non-steroidal anti-inflammatory drug (NSAID). Hence, for example, it is not included in the lists of such drugs published in (a) the Merck Index, (Budavari, 1989, pages THER-15 to THER-16), (b) Scientific American (Weissmann, 1991, page 86), and (c) Understanding Arthritis (Kushner, 1984, pages 52-53). Likewise, p-aminobenzoic acid is not recognized as being a "slow acting" anti-inflammatory agent (Understanding Arthritis, Kushner, 1984, pages 55-57). Indeed, in a feature article entitled "The new scoop on vitamins," Time magazine (Toufexis, 1992) failed to make any reference whatsoever to PABA.

SUMMARY OF THE INVENTION

These and other objects of this invention are achieved by providing a novel method for clinical treatment of chronic inflammatory diseases. This invention involves use of orally administered amine and amine-related derivatives of benzoic acid as carbonyl trapping agents. These primary therapeutic agents act by chemically binding to and sequestering the aldehyde and/or ketone products of lipid peroxidation. Increased levels of lipid peroxidation have been repeatedly demonstrated as a part of the "inflammatory cascade" process which underlies the secondary etiology of chronic inflammatory diseases.

p-Aminobenzoic acid is an example of the primary absorbable pharmacological agent of the present invention. PABA has a small molecular weight, is water soluble, has a primary amino group which should react with carbonyl-containing metabolites under physiological conditions and is tolerated by the body in relatively high dosages and for extended periods. The present invention sets forth the belief that carbonyl sequestering agents administered in oral dosages may be used in combination with co-agents consisting of proven antioxidant free radical trapping agents, and agents related thereto, so as to produce a synergistic physiological effect of an anti-inflammatory and analgesic nature. Co-agents of the present invention include antioxidants (such as alpha-tocopherol), suspending reagents (such as carboxymethyl cellulose), other vitamins, vitamin-related agents (such as carnitine), chemical conjugating agents which may facilitate kidney drug elimination (such as glycine), and orally administered non-absorbable polyamine or polyamine-related agents (such as chitosan).

1. Aims of the Invention

Accordingly, it is a general object of this invention to treat the symptomology of chronic inflammatory diseases and etiologically related symptomology by use of carbonyl trapping agents in combination with known antioxidant free radical

trapping co-agents and factors related thereto, so as to create compositions with additive, complimentary physiological therapeutic characteristics. It is a further object of this invention to facilitate the effectiveness of this anti-inflammatory and analgesic procedure by use of orally consumed carbonyl trapping agents which are of a non-absorbable nature, so as to bind and sequester carbonyl chemical agents which are present in food, thus preventing such toxic agents from being absorbed into the body.

In particular, it is an object of the present invention to use absorbable amino and amine-related primary agents, non-absorbable amino and amine-related polymeric co-agents, co-agents which inhibit lipid peroxidation, vitamin co-agents which may be inadvertently depleted, vitamin-related co-agents, co-agent metabolites which may be depleted within the body, sulphhydryl co-agents, co-agents which may facilitate glutathione activity, so as to improve upon the prior art.

It is an object of the present invention that the drug compositions described herein may provide clinical value in the treatment of disease symptomology for disorders featuring lipid peroxidation and resultant formation of toxic carbonyl compounds, including: chronic gingivitis, chronic periodontitis, chronic autoimmune gastritis, ileitis, colitis, interstitial cystitis, arthritis, tendinitis, carpal tunnel syndrome and other cumulative trauma disorders, systemic lupus erythematosus, autoimmune vasculitis, asbestosis, silicosis, chronic obstructive pulmonary disease, chronic obstructive pulmonary disease, Lyme disease, inflammatory myopathies, status epilepticus, inflammatory neuropathies, myasthenia gravis, multiple sclerosis, as well as lessening of inflammatory site edema, and post-event ischemia and reperfusion injury resulting from acute central nervous system trauma, stroke, kidney ischemia or myocardial infarction.

It is another object of the present invention that in so far as the therapeutic procedures described herein may serve to delay

the necessity of initiating the use of known medicaments or to decrease the dosages of known medicaments required to achieve beneficial effects, the period of prior art drug therapeutic value may be extended and detrimental clinical side effects resulting from use of known medicaments may be decreased, so that overall patient treatment may be improved.

It is a further object of this invention that the absorbable amine and amine-related substances and derivatives thereof described herein when used in combination with specified co-agents may be clinically applied to treat veterinary disorders comparable to at least some of those human disorders described above.

2. Statement of Invention

It is known that aldehyde chemical metabolites, which contain carbonyl functional groups, are generated during the process of chronic inflammation. These aldehyde products result from pathologically increased lipid peroxidation, which may be initiated by a variety of activated oxygen chemical species such as the hydroxyl radical, HO[•] (Halliwell and Gutteridge, 1985, pp. 119-120). The reactive cascade of free radical propagation → lipid peroxidation → aldehyde formation and other subsequent effects of inflammation is well documented in the prior art (Halliwell and Gutteridge, 1985, pp. 102-103).

The concept of using carbonyl-trapping agents such as primary amine or amine-related derivatives of benzoic acid to treat chronic inflammatory diseases has not been recognized or disclosed. Thus, the application of this principle in conjunction with use of known antioxidant free radical trapping agents to produce new and novel compositions which have improved, synergistic therapeutic properties also has not been recognized. When compared to previously disclosed understanding of the actions of recognized non-steroidal anti-inflammatory drugs (Weissmann, 1991), it is evident that the inventive concept

described herein represents a new approach to the treatment of chronic inflammatory disorders.

Previously, attempts at pharmaceutical intervention in this cascade of inflammatory reactions has focused primarily on use of both water-soluble and lipid-soluble antioxidant free radical trapping agents or use of metal chelating agents (Halliwell and Gutteridge, 1985, pp. 125 and 116-117). As iron and copper ions have been shown to induce hydroxyl radical formation (Halliwell and Gutteridge, 1985, pg. 123) and induce lipid peroxidation (Halliwell and Gutteridge, 1985, pg. 124), the use of metal chelating agents such as desferoxamine to ameliorate the inflammatory cascade has received some attention (Halliwell and Gutteridge, 1985, pp. 116-117). However, desferoxamine has predictable ocular and auditory side effects (Halliwell and Gutteridge, 1985, pgs. 117 and 140), and present examples of antioxidant free radical trapping agents and combinations thereof have proven to be of limited clinical value.

Both PABA and penicillamine are primary amine agents which also function as antioxidant free radical trapping agents. Yet as antioxidant agents PABA and penicillamine are presently regarded as being of secondary, nominal value, due either to weak antioxidant properties or toxic side effects, respectively. Thus their use as anti-inflammatory agents has been quite limited. Their potential value for trapping the aldehyde products of inflammation-related lipid peroxidation has never been recognized. Hence the formulation of a new composition, such as one having PABA as its primary agent, known antioxidant free radical scavenging chemicals as co-agents and lacking vitamin C, has never been previously described, and the potential for clinical use of such a novel composition in treatment of chronic inflammatory diseases never recognized.

Further distinctions should be made between the present invention and previously recognized use of penicillamine, one of the "slow-acting" anti-inflammatory drugs mentioned in Understanding Arthritis (Kushner, 1984), a publication of the Arthritis

Foundation. The primary amino and amino-related principle agents described in the present invention are all derivatives of aminobenzoic acid, which should facilitate their safe elimination from the body by normal kidney filtration. Penicillamine is not a derivative of aminobenzoic acid. In addition, penicillamine has a reduced sulphydryl group, unlike any of the primary agents claimed herein. However, penicillamine does have a primary amino functional group as well as a carboxylic acid functional group, like aminobenzoic acid. In Understanding Arthritis Kushner noted that:

Many doctors believe that the slow-acting drugs may slow the underlying disease, though how they do this is not clear. This group of drugs includes gold, penicillamine, cytotoxic, and antimalarial drugs. All of the drugs in this group have to be taken for many weeks, and often for several months, before their full effects become noticeable. The relief they provide may last for some time after they are no longer being taken. But with these benefits of long-lasting relief and a possible slowing of the disease also comes a higher risk of serious side effects... (pages 55-56) ... Again, the side effects [of penicillamine] often require some people to stop taking this drug. Like gold, penicillamine may damage the kidneys and bone marrow, and may also cause fever, chills, rashes, sores in the mouth, a sore throat, stomach upset, muscle weakness, loss of taste, and easy bruising or bleeding. Because of these possible side effects, the drug is taken only with close supervision by a doctor... (page 57)

The present invention constitutes an alternative slow-acting anti-inflammatory composition which is believed to be inherently safer for the patient and act via a mechanism not previously recognized or described.

A review of the article by Weissmann (Scientific American, 1991, pages 84-90) will serve to illustrate the distinction between

the present invention and prior art development of non-steroidal anti-inflammatory drugs. In discussing presently recognized understanding of the actions of NSAIDs, Weissmann stated, in part:

NSAIDs act by blocking the production of both PGG, and PGH₂. Platelets transform the latter into a most potent vasoconstricting and platelet-aggregating substance, thromboxane B₂... (page 87)
...Aspirin irreversibly inactivates PGH synthase [i.e., prostaglandin H synthase]. Platelets cannot make more synthase and so make no more thromboxane...less than one tablet a day can irreversibly block the PGH synthase activity of platelets... (page 88)

Vane's theory that the local production of prostaglandins leads to inflammation has only partly been substantiated, however... aspirinlike drugs exert clinical effects that do not depend on inhibiting prostaglandin synthesis... (page 88)

The broad spectrum of NSAID effects most likely results from their physical properties, which permit them to disrupt interactions within biological membranes... For example, aspirin alters the uptake of fatty acids and their insertion into the membranes of cultured human monocytes and macrophages. Salicylates also inhibit anion transport across a variety of cell membranes. Finally, NSAIDs inhibit bone metabolism and the synthesis of proteoglycan, a substance that forms the matrix of cartilage... (page 88)

Recent work in my laboratory has uncovered an alternative mechanism for the effects of aspirinlike drugs: interference with stimulus-response coupling in neutrophils, the most abundant cells of acute inflammation. These cells are the first line of defense against foreign intruders and among the first to cause injury in autoimmune diseases like rheumatoid arthritis. They damage tissues by releasing enzymes that break down

proteins (proteases), as well as inflammatory peptides, reactive oxygen species such as O_2^- and H_2O_2 (peroxide), and lipid irritants such as platelet-activating factor and leukotriene B₄. (pages 88-89)

...Both 'homotypic' adhesion between neutrophils and 'heterotypic' adhesion of neutrophils to the walls of blood vessels are required for cells to make their way out of the circulatory system and to cause inflammation... It is therefore likely that the anti-inflammatory effect is related to the ability of both [sodium salicylate and aspirin] compounds to inhibit homotypic and heterotypic adhesion in neutrophils rather than to their unequal effect on prostaglandin synthesis...

All NSAIDs inhibit the homotypic adhesion of neutrophils, but they differ in their effects on other functions of the neutrophil... (page 89)

Some of the effect of NSAIDs on cells arises from interference with the binding of chemoattractants and other stimuli. These drugs inhibit the binding of at least some of these ligands with their receptors in the cell membrane... NSAIDs interfere in particular with signals that depend on so-called G proteins for transduction through cell membranes. (page 90)

The present invention, by contrast, depends on a fundamentally different mechanism of action. The present invention is based on use of primary amine or amine-related derivatives of benzoic acid as principle agents for chemically binding to and sequestering aldehyde products of inflammation site lipid peroxidation in combination with previously recognized antioxidant free radical trapping co-agents. This unique, multiple-level approach to interference with certain steps in the inflammatory cascade has not been previously recognized by other research investigators.

This is, in fact, the first anti-inflammatory agent invention which addresses the issue of aldehyde formation at inflammation sites. As aldehydes are highly reactive molecules capable of

reacting with proteins, lipids and nucleic acids (Jollum and coworkers, 1973, pg. 200; Carden and coworkers, 1986), their increased formation at inflammation sites may be a significant contributing factor in the evolution of the clinical pathology of inflammatory disorders. Halliwell and Gutteridge (1985, pg. 123) noted that malonaldehyde

...is only one of a great number of carbonyl compounds formed in peroxidising systems and often is only a tiny percentage of the total products formed...Other toxic aldehydes include 4,5-dihydroxydecanoal and 4-hydroxynonenal. Lipid peroxides and/or cytotoxic aldehydes derived from them can block macrophage action, inhibit protein synthesis, kill bacteria, inactivate enzymes, crosslink proteins and generate thrombin....

The results of several published research studies suggest that dysfunctional lipid peroxidation may be a contributing factor in the etiology of a variety of chronic inflammatory diseases, such as rheumatoid arthritis (Rowley and coworkers, 1984), multiple sclerosis (Hunter and coworkers, 1985), silicosis (Katsnelson and co-workers, 1989, pg. 318), Duchenne muscular dystrophy (Kar and Pearson, 1979; Jackson and coworkers, 1984), and chronic inflammatory bowel disease (Ahnfelt-Ronne and coworkers, 1990). As exposure to asbestos fibers can stimulate lipid peroxidation (Halliwell and Gutteridge, 1985, pg. 152), asbestosis should also be included in this category. Increased lipid peroxidation has also been demonstrated in acute central nervous system trauma (Hall, 1987, pgs. 421 and 424; Demopoulos and coworkers, 1980, pg. 97; Kontos and coworkers, 1981, pg. 2329), as a result of stroke (Zivin and Choi, 1991, pg. 61) and subsequent to myocardial infarction (Kurdin, 1978). Status epilepticus is one of several clinical disorders which have been linked to increased intracellular concentrations of free radicals, with subsequent lipid peroxidation (Del Maestro, 1980, pg. 163). Likewise, published evidence has documented the ability of carbonyl compounds resulting from lipid peroxidation to induce foot edema in the rat (Benedetti and coworkers, 1980).

(3) Detailed Description of the Preferred Embodiment

The inventive feature disclosed in this text is that compositions consisting of absorbable carbonyl trapping drugs in combination with known antioxidant free radical trapping co-agents may be of particular synergistic benefit in preventing or ameliorating forms of chronic inflammation by incorporating two pharmacological strategies, the sequestering of cytotoxic aldehydes and ketones generated at sites of chronic inflammation and the sequestering of activated oxygen chemical species generated earlier in the inflammatory cascade. It is further understood that oral use of non-absorbable carbonyl trapping agents may serve to prevent absorption of dietary aldehydes and ketones from the alimentary tract into the body, thus complementing the intended therapeutic results.

(i) Mechanism of Action of Primary Agents

For the most part, these pharmacological reactions are based on the ability of primary amine compounds to react with aldehyde functional groups of potentially toxic agents, yielding covalently bound Schiff base products. Several examples of chemically analogous reactions, presented within other contexts, have been publicly presented. Representative examples are discussed below. These model chemical systems are directly analogous to the proposed mechanism of drug action which is the basis of the present invention.

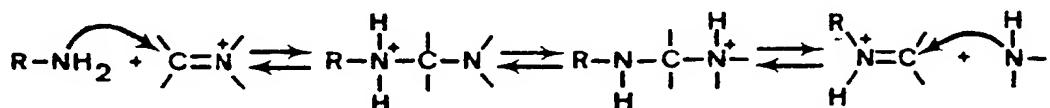
Comments by Feeney and coworkers (1975, pg. 141) provide an appropriate introduction to this subject:

A wide variety of substances with -NH₂ groups condense with carbonyl compounds... This condensation of primary amines with aldehydes and ketones to give imines was first discovered by Schiff (1900). The overall equilibrium greatly favors hydrolysis in aqueous solution for aliphatic aldehydes. With

aromatic aldehydes, the equilibrium is shifted in favor of Schiff base formation. It is important to note that increasing the nucleophilic strength of the amine will increase the rate of the carbonyl-amine reaction but will have almost no effect on the position of the equilibrium.

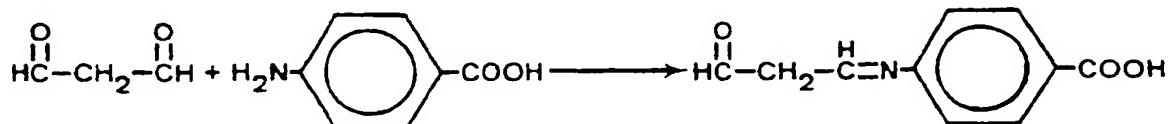
These comments suggest that the amine-containing carbonyl-trapping drugs described herein should have particular promise for binding furanalddehydes, which are aromatic. These comments also suggest that doses of absorbable amine drugs may require *in vivo* concentrations in the range of 1:100 to 1:1,000 (carbonyl:amine) in order to achieve clinical effectiveness. This, in turn, suggests that therapeutic dosages may lie in the range of grams per day and that only drugs of particularly low toxicity will have human applications.

Fecney and coworkers (1975, pg. 144) also noted the phenomenon of Schiff base transimination, which occurs to a significant extent at neutral pH:



The existence of such non-enzymatic reversible transimination reactions is important within the context of this invention, as it suggests that *in vivo* both bound carbonyl agents, in addition to free carbonyl agents, may be sequestered by amine-containing drugs.

(a) The direct *in vitro* addition of p-aminobenzoic acid or ethyl p-aminobenzoate to malondialdehyde or its tautomer, beta-hydroxyacrolein, has been described (Sawicki and coworkers, 1963).

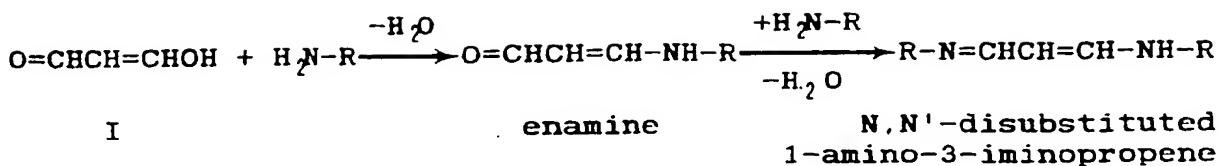


This report also described the reaction of aminobenzene (that is, aniline) with malonaldehyde. The metabolic fate of PABA in humans has been actively investigated and well reported in the biomedical literature (Young and coworkers, 1971; Howie and Bourke, 1979). It is so actively metabolized via several mechanisms and quantitatively removed in urine (Weizman and coworkers, 1985; Bingham and Cummings, 1983) that PABA excretion has become a widely recognized standard for measuring urinary clearance. Small amounts of PABA are normally present in the human diet. It is recognized as being a vitamin for many organisms and is classified as a member of the vitamin B complex (Smith, 1976, pg. 194; Winitz and coworkers, 1970, pgs. 527-528; Scott and Robbins, 1942). As a vitamin for human use PABA is commercially marketed in the United States in the dosage range of 5 to 550 mg/day.

(b) Self-polymerization of o-aminobenzaldehyde has been described. In the 1993 edition of the Sigma Chemical Company catalog of biochemical reagents the following statement appears on page 87 of its listing: "***o*-AMINOBENZALDEHYDE** Unstable! [store at] -20°C Polymerizes rapidly when exposed to room temperature. May yield slightly hazy solution in ethanol due to presence of a small amount of polymer. Shipped in dry ice." This information directly indicates that a primary amino group covalently linked to a benzene ring possesses sufficient reactivity for significant reaction with aldehyde functional groups at room temperature. It is apparent that no form of activation of the amino group is required and that a Schiff base product forms readily.

(c) The direct in vitro addition of n-hexylamine to beta-hydroxyacrolein to produce an N,N'-disubstituted 1-amino-3-iminopropene derivative has been reported (Chio and Tappel, 1969). The reaction may be represented as follows:

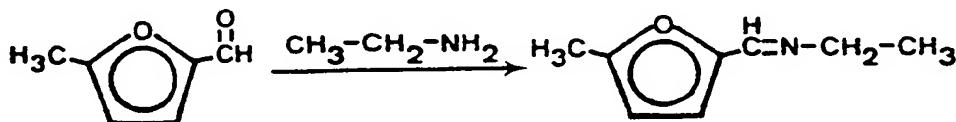
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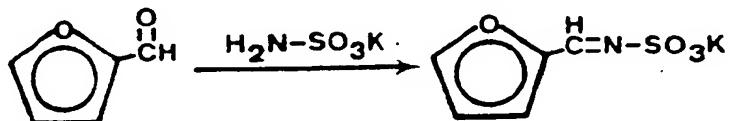
where I = **beta**-hydroxyacrolein

R = -(CH₂)₅-CH₃

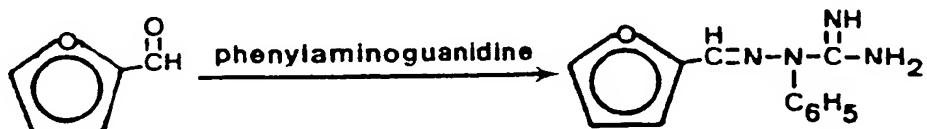
(d) The direct chemical addition of amines to 5-methyl-2-furfural has been described (Holdren and Hixon, 1946). A wider variety of aliphatic and aromatic primary amines can add to furfural in this manner, yielding Schiff base products (Dunlop and Peters, 1953, pg. 353).



(e) As described by Dunlop and Peters (1953, pg. 373) earlier work demonstrated the ability of furfural to react with amino-sulfonic salts to produce furfurylideneaminosulfonates.



(f) The reaction of phenylaminoguanidine with furfural (Dunlop and Peters, 1953, pg. 371) may serve as an example of covalent furanaldhyde trapping with a hydrazine.

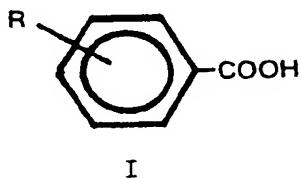


It is proposed that the small molecular weight, absorbable, primary amine drugs and amine-related drugs described herein will have analogous behavior *in vivo*; as well as an additional characteristic which will facilitate disposal as urine metabolites. All of these drugs contain a carboxylic acid group to

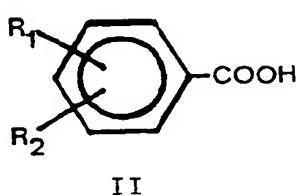
facilitate uptake and processing by the kidneys.

(ii) Examples of Absorbable Drug Primary Agents

For any carboxylic acid primary agent listed herein as useful in the present invention, it is believed that the salt forms, free acid form, ester derivatives, amide derivatives and analogous non-aromatic benzene ring derivative (that is, cyclohexane carboxylic acid derivative) thereto will also be useful. The class of primary agents (molecular weight range 100 to 1,400) of the present invention may be summarized as noted below in chemical structures I, II and III.



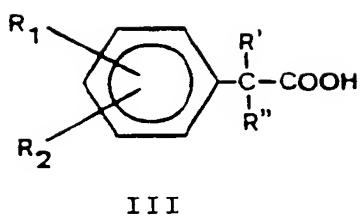
$R = -NH,$
 -aminoalkyl group having
 1-10 carbons including
 hydrocarbon isomers
 and/or hydroxylated
 derivatives thereof
 $-NHC(=NH)NH_2,$
 $-(CH_2)_nNHC(=NH)NH_2$
 where $n = 1-10$
 $-C(=NH)-NH_2,$
 $-(CH_2)_n-CH=NC(=NH)NH_2$
 where $n = 1-10$
 $-NHC(=NH)NHNH_2,$
 $-(CH_2)_nNHC(=NH)NHNH_2$
 where $n = 1-10$
 $-(CH_2)_n-CH=NC(=NH)NHNH_2$
 where $n = 1-10$
 $-NHNHC(=NH)NH_2,$
 $-(CH_2)_n-NHNHC(=NH)NH_2$
 where $n = 1-10$
 $-(CH_2)_n-CH=N-NHC(=NH)NH_2$
 where $n = 1-10$



$R_1 = -NH,$
 -aminoalkyl group
 (1-10 carbons)
 including hydrocarbon
 isomers and/or
 hydroxylated
 derivatives thereof
 $-(CH_2)_nNHC(=NH)NH_2,$
 where $n = 1-10$
 $-C(=NH)-NH_2,$
 $-(CH_2)_n-CH=NC(=NH)NH_2$
 where $n = 1-10$
 $-NHC(=NH)NHNH_2,$
 (continued)

$\cdots (\text{CH}_2)_n \text{NHC}(=\text{NH})\text{NNNH} \cdots$
 where $n = 1-10$
 $\cdots (\text{CH}_2)_n \text{CH}=\text{NC}(=\text{NH})\text{NNNH} \cdots$
 where $n = 1-10$
 $\cdots \text{NNHC}(=\text{NH})\text{NH} \cdots$
 $\cdots (\text{CH}_2)_n \text{NNHC}(=\text{NH})\text{NH} \cdots$
 where $n = 1-10$
 $\cdots (\text{CH}_2)_n \text{CH}=\text{N} \cdots \text{NHC}(=\text{NH})\text{NH} \cdots$
 where $n = 1-10$

$\text{R}_2 = \begin{aligned} &-\text{NH}_2 \\ &-\text{OH} \\ &-\text{O}-\text{CH}_3 \\ &-\text{O}-\text{R}' \text{ with alkyloxy} \\ &\text{group R' having 2-10} \\ &\text{carbons including} \\ &\text{hydrocarbon isomers} \\ &\text{and/or hydroxylated} \\ &\text{derivatives thereof} \\ &-\text{aminoalkyl group} \\ &(1-10 \text{ carbons}) \\ &\text{including hydrocarbon} \\ &\text{isomers and/or} \\ &\text{hydroxylated} \\ &\text{derivatives thereof} \\ &-\text{SO}_2\text{H} \\ &-\text{CH}_3 \\ &-(\text{CH}_2)_n \text{CH}_3 \text{ where } n = 1-10 \\ &\text{including hydrocarbon} \\ &\text{isomers and/or} \\ &\text{hydroxylated} \\ &\text{derivatives thereof} \end{aligned}$



$\text{R}_1 = \begin{aligned} &-(\text{CH}_2)_n \text{-NH, where } n = 0-10} \\ &\text{including isomers of} \\ &\text{the aminoalkyl group} \\ &\text{and hydroxylated} \\ &\text{derivatives thereof} \\ &-\text{C}(=\text{NH})-\text{NH}_2 \\ &-\text{NHC}(=\text{NH})\text{NH}_2 \\ &-(\text{CH}_2)_n \text{NHC}(=\text{NH})\text{NH}_2 \\ &\text{where } n = 1-10 \\ &-(\text{CH}_2)_n \text{CH}=\text{NC}(=\text{NH})\text{NH}_2 \\ &\text{where } n = 1-10 \\ &-\text{NHC}(=\text{NH})\text{NNNH}_2 \\ &-(\text{CH}_2)_n \text{NHC}(=\text{NH})\text{NNNH}_2 \\ &\text{where } n = 1-10 \\ &-(\text{CH}_2)_n \text{CH}=\text{NC}(=\text{NH})\text{NNNH}_2 \\ &\text{where } n = 1-10 \\ &-\text{NNHC}(=\text{NH})\text{NH}_2 \\ &-(\text{CH}_2)_n \text{NNHC}(=\text{NH})\text{NH}_2 \\ &\text{where } n = 1-10 \\ &-(\text{CH}_2)_n \text{CH}=\text{N} \cdots \text{NHC}(=\text{NH})\text{NH}_2 \\ &\text{where } n = 1-10 \end{aligned}$
 (continued)

$R_2 =$ -NH₂
-H
-OH
-O-CH₃
-O-R₃ where R₃ has 2-10 carbons including hydrocarbon isomers and/or hydroxylated derivatives thereof
-aminoalkyl group (1-10 carbons) including hydrocarbon isomers and/or hydroxylated derivatives thereof
-SO₂H
-CH₃
-(CH₂)_nCH₃ where n = 1-10 including hydrocarbon isomers and/or hydroxylated derivatives thereof

$R' =$ -H
-CH₃
-OH

$R'' =$ -H
-CH₃
-OH

(iii) Mechanism of Action of Non-Absorbable Primary Amine and Amine-Related Agents

The presence of aldehydes and ketones in the human diet may be a factor which may put the patient suffering from a chronic inflammatory disease further at risk. This might be especially important for victims of ileitis and colitis, as the damaging effects of inflammation site carbonyl compounds may be accentuated by direct exposure to dietary carbonyl agents. 5-Methyl furfural has been identified in the oil of roasted coffee and in oil of cloves (Dunlop and Peters, 1953, pg. 403). 5-Hydroxymethyl furfural has been found in sherry, port and brandy alcoholic beverages: honey and other sugar syrup products (Levitt and coworkers, 1985). Levels of furfural (that is, 2-furanaldehyde or 2-furancarboxaldehyde) and 5-hydroxymethyl-2-furanaldehyde (that is, 5-hydroxymethyl furfural) as high as 4.5 mg/L and 93.2

mg/L, respectively, have been found in wine products (Shimizu and Watanabe, 1979). Furfural has also been detected in beer and distilled liquors (Dunlop and Peters, 1953, pg. 308), as well as in natural oil products such as oil of lime (Dunlop and Peters, 1953, pg. 280). Summarizing earlier work, Rice (1972) noted:

Small quantities of furfural occur in many foodstuffs, including - among many others - bread, coffee, processed fruits and fruit juices, and alcoholic beverages. In fact, whenever plant or animal tissue containing pentoses or hexoses is subjected to heat, the possibility arises that furfural, 5-hydroxymethyl furfural, and probably other furans as well will be produced.

Pettersen and Jollum (1972) referred to earlier work which demonstrated the generation of 2-furanaldehyde, 5-hydroxymethyl-2-furanaldehyde and 2,5-furandicarboxaldehyde during bread baking. In his food chemistry study, Baltes (1985) noted the presence of furfural in curing smoke tar; and the presence of furfural, 5-methyl-2-furfural, dihydrofuranone, 5-hydroxymethyl-2-furfural and 2,5-furandialdehyde in caramels. Baltes also examined the products obtained by Maillard reaction of glucose and phenylalanine and identified furfural and 2,5-di-(hydroxymethyl)-furan among the main components. Thus various furan aldehyde compounds have been identified in the human diet.

In addition, a wide variety of naturally occurring non-aromatic and aromatic aldehydes and ketones have been found in fruits and vegetables (Schauenstein and Esterbauer, 1977, pgs. 181-194). These include alkanals, alk-2,4-dienals, alk-2-enals, alk-1-en-3-ones, alpha-dicarbonyl compounds, beta-dicarbonyl compounds alkan-2-ones. Schauenstein and Esterbauer have noted, in part, that:

Aliphatic carbonyl compounds represent the most important group of flavouring compounds in our

foodstuffs. One finds them in all flavour extracts. They are either entirely, or in large measure, responsible for nearly all known flavours and determine, even when present in small amounts, the taste and odour of our foodstuffs, and beverages such as tea and coffee... (pg. 189)

As the presence of carbonyl agents in the diet is not restricted to fruits and vegetables, Schauenstein and Estabauer have further noted that:

Unsaturated aldehydes also arise through thermal degradation of carbohydrates, amino acids, and fats. Such thermal degradative processes are probably responsible for the presence of these aldehydes in boiled, fried, and baked foods. Unsaturated aldehydes have been detected in a large number of foodstuffs, such as potatoes, potato chips, poultry, meat, fish, salad oils, bread, and bakery products ... (pgs. 193-194)

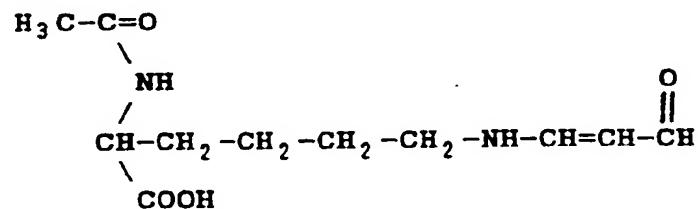
As such, it is apparent that the diet is a significant source of carbonyl agents, and their presence may be a contributing factor in the etiology of chronic inflammatory diseases. Toxic properties of aliphatic aldehydes are well known, and toxic properties of furanaldehyde derivatives have been demonstrated in both in vivo and in vitro studies (Konecki and coworkers, 1974; Ulbricht and coworkers, 1984).

It is proposed that non-absorbable dietary supplements such as those defined below can be of health benefit by virtue of their ability to covalently trap dietary aldehydes and ketones. The agents described in this section can accomplish this function because they bear primary amine groups or derivatives thereof. As large molecular weight molecules which are non-digestible they have the capacity to pass through the digestive tract, acting in effect as another form of dietary fiber. These non-absorbable substances may be divided into three classes: (1)

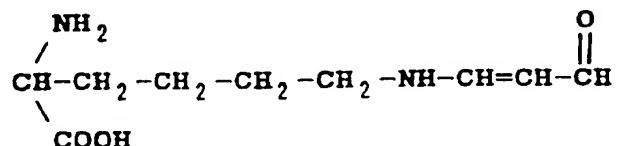
naturally occurring polyamine polysaccharides, (2) chemical derivatives of naturally occurring polysaccharides, and (3) synthetic polyamine polymers.

The fate of malondialdehyde given orally to rats may serve as an example of the metabolism of dietary aldehydes, and how an understanding of this process can be used to define non-absorbable carbonyl-trapping drugs. Studies by Draper and coworkers (1986) demonstrated that the primary form of "bound" MDA in rat or human urine is N-alpha-acetyl-epsilon-(2-propenal)lysine. This is the biologically alpha-N acetylated derivative of the MDA-lysine adduct N-epsilon-(2-propenal)lysine, as shown below.

Draper and coworkers (1986) were able to generate N-epsilon-(2-propenal)lysine in vitro by exposing beef muscle protein to MDA, followed by treatment with pepsin and hog intestinal juice. This indicates that the epsilon-amino groups of dietary protein



N-alpha-acetyl-epsilon-(2-propenal)lysine



N-epsilon-(2-propenal)lysine

lysine residues can covalently bind dietary aldehyde under conditions found in the intestinal tract. As such, chemically analogous primary amino groups on non-absorbable drugs should also be capable of covalently binding dietary aldehydes under conditions to be found in the intestinal tract. In this case, however, the bound carbonyl species would be excreted in the feces, thus preventing subsequent in vivo exposure to dietary

carbonyl agents.

In their study Drapier and coworkers noted that N-alpha-acetyl-epsilon-(2-propenal)lysine was found in urine of fasted rats or animals fed on MDA-free diets, indicating that the MDA-lysine adduct also forms in vivo. These investigators referred to earlier work which demonstrated that the MDA concentration normally found in food is in the range of <0.1 to 10 ppm (0.1 to 10 μ M), which gives some idea of dietary aldehyde concentrations.

(iv) Examples of Non-Absorbable Drug Products Useful in the Present Invention

(a). Naturally Occurring Amino-Containing Polysaccharides

Any naturally occurring polysaccharide featuring beta-1,2, beta-1,3, beta-1,4 and/or beta-1,6 linkages which contains amino-sugars may be regarded as a non-digestible, potentially active carbonyl trapping agent. The chitin class of biopolymers may be cited as an example of such an agent, having the general structure of poly-beta-(1 \rightarrow 4)-N-acetyl-D-glucosamine. A form of microcrystalline chitin has been described in which some of the acetyl groups have been removed, revealing free amino groups (Austin and coworkers, 1981, pg. 750). Chitins obtained from different sources feature different degrees of amino deacetylation (Austin and coworkers, 1981, pg. 752).

(b). Chemical Derivatives of Naturally Occurring Polysaccharides

Various pretreatment procedures may be applied to naturally occurring polysaccharides prior to generation of chemical derivatives. Generation of microcrystalline polysaccharides is one example of such a pretreatment procedure. As applied to cellulose or chitin (Yalpani, 1988, pg. 389), this yields a colloidal processed form of polysaccharide featuring high porosity and enhanced susceptibility to chemical reactions. Generation of "microfibrillated" cellulose or chitin is another example of a

pretreatment procedure which produces enhanced surface area, increased water retention capacity and enhanced chemical accessibility (Yalpani, 1988, pg. 390). Use of strong (> 18%) sodium hydroxide is still another recognized pretreatment, or activation, procedure found to be helpful as a starting point for preparing chemical derivatives of polysaccharides (Yalpani, 1988, pg. 214).

(b)(1). Deacetylation of Naturally Occurring Polysaccharides

A variety of polysaccharides have been identified which are rich in N-acetylated residues. Upon chemical deacetylation these carbohydrates yield high molecular weight derivatives bearing primary amino groups directly linked to sugar carbons, that is, no sidearm spacer units present.

(i) Chitosan. This is the deacetylated form of chitin. As described in the Merck Index (Budavari and coworkers, 1989, pg. 316) chitin is a cellulose-like biopolymer the composition of which consists mostly of N-acetyl-D-glucosamine residues covalently linked by beta-1,4 bonds. Chemical deacetylation removes acetate, generating primary amine groups still covalently bound to the polysaccharide. Chitosan has recognized uses in water treatment, in photographic emulsions, and in improving the dyability of synthetic fabrics and fibers. The free amine groups in this substance also give it chelating properties (Austin and coworkers, 1981).

(ii) Chondroitin sulfate. This is a mucopolysaccharide found commonly in mammalian tissue. It consists of repeating disaccharide units, each of which has a D-glucuronic acid residue beta-1,4 linked to an N-acetylchondrosine residue (Merck Index, Budavari and coworkers, 1989, pg. 344).

(iii) Hyaluronic acid. This mucopolysaccharide is also found commonly in mammalian tissues. It consists of glucuronic acid and glucosamine residues bound by beta-1,3 and beta-1,4 linkages (Merck Index, Budavari and coworkers, 1989, pp. 751-752).

(iv) Keratan sulfate. This mammalian glycosaminoglycan consists of a repeating disaccharide unit of a C-6 sulfated C-2 N-acetylated sugar residue and a galactose residue linked by beta-1,4 bonds (Yalpani, 1988, pp. 27-28).

(b)(2). Chemical Amination of Polysaccharides

(i) 2-Amino-2-deoxy-cellulose. Cellulose can be aminated by a process of selective oxidation, oximation and subsequent reduction with lithium aluminum hydride (Yalpani, 1988, pp. 281-282).

(ii) Alternative amination procedures. Aminodcoxy polysaccharides can also be prepared via azide or hydrazide intermediates or by reductive amination using sodium cyanoborohydride (Yalpani, 1988, pg. 281). Besides being applied to cellulose, other non-digestible polysaccharides such as curdlan (Yalpani, 1988, pg. 22) may be aminated by such chemical procedures.

(iii) 3-Aminopropylcellulose. Reaction of cyanoethylcellulose with borane-tetrahydrofuran or borane-dimethyl sulfide complexes in tetrahydrofuran generates 3-aminopropylcellulose (Yalpani, 1988, pgs. 250 and 255). In this derivative each primary amine group is at the end of a three carbon sidearm.

(iv) Aminoethylcellulose. This chemical has been previously marketed as an anion exchange column chromatography resin (Sigma Chemical Co. catalog, Feb. 1981) and used as such in protein purification studies (Fasold, 1975, pp 481-482).

(v) Other aminoalkyl-, amino(hydroxyalkyl)-, aminoalkyl-ether-, and amino(hydroxyalkyl)-ether- derivatives of cellulose, chitin and other naturally occurring non-digestible carbohydrates. Noting that the chemical methodology for producing such derivatives is documented in public domain literature, the biomedical application of such derivatives for therapeutic purposes described herein is also claimed. This would include:

aminoalkyl derivatives of the formula

$\text{H}_2\text{N}-(\text{CH}_2)_n-\text{[carbohydrate]}$ where $n = 1 - 10$, including alkyl isomers;

amino(hydroxyalkyl)- derivatives derivatives of the formula

$\text{H}_2\text{N}-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $m = 0 - 10$
 $n = 0 - 10$;

aminoalkyl-ether- derivatives of the formula

$\text{H}_2\text{N}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$, where $n = 1 - 10$; and

amino(hydroxyalkyl)-ether- derivatives of the formula

$\text{H}_2\text{N}-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$, where $m = 0 - 10$
 $n = 0 - 10$

(vi) Aminobenzyl- derivatives of cellulose, chitin or other naturally occurring non-digestible carbohydrates. As the aromatic amine group is a weaker base than its aliphatic counterpart, this class of non-absorbable amines should be less chemically active than amino- and aminoalkyl- derivatives described above. These derivatives are of the following general structures:

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{CH}_2-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$ where $n = 0 - 10$; and

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$
 $\text{where } m = 0 - 10$
 $n = 0 - 10$

This includes p-, o- and m-benzene ring amino- and aminomethyl-isomers, and alkyl group isomers.

(vii) guanidine and aminoguanidine derivatives of cellulose, chitin or other naturally occurring non-absorbable carbohydrates selected from the group consisting of:

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{O}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$,

including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-[\text{carbohydrate}]$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-[\text{carbohydrate}]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-\text{O}-[\text{carbohydrate}]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{N}=\text{CH}-(\text{CH}_2)_n-[\text{carbohydrate}]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{N}=\text{CH}-(\text{CH}_2)_n-\text{O}-[\text{carbohydrate}]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{NH}-[\text{carbohydrate}]$;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-[\text{carbohydrate}]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-\text{O}-[\text{carbohydrate}]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{N}=\text{CH}-(\text{CH}_2)_n-[\text{carbohydrate}]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{N}=\text{CH}-(\text{CH}_2)_n-\text{O}-[\text{carbohydrate}]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{NH}-[\text{carbohydrate}]$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{NH}-(\text{CH}_2)_n-[\text{carbohydrate}]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{NH}-(\text{CH}_2)_n-\text{O}-[\text{carbohydrate}]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{N}=\text{CH}-(\text{CH}_2)_n-[\text{carbohydrate}]$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

thereof; and

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{N}=\text{CH}- (\text{CH}_2)_n-\text{O}-[\text{carbohydrate}]$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof

(b) (3). Aminated Sucrose Polyesters

Mixtures of fatty acid hexa-, hepta- and octaesters of sucrose, known as sucrose polyester, are not hydrolyzed by pancreatic lipase enzymes and are not absorbed in the intestine (Jandacek, 1984). It is proposed and claimed herein that primary amines, aminoguanidine and guanidine derivatives of sucrose polyesters may be of benefit in reduction of dietary carbonyl substances, analogous to the proposed action of other non-absorbable agents described herein. Such derivatives of sucrose polyesters would include structures in which the carbonyl trapping functional group is in the omega-, omega-1 or other isomeric position(s) within the fatty acyl chains, fatty acyl chains having more than one nitrogen functional group and fatty acyl chains having hydroxyl groups. Such aminated sucrose polyesters may be used in pure form as a dietary supplement, or may be prepared as a coating on a particulate carrier such as cellulose or styrene divinylbenzene copolymer resin.

(c). Synthetic Polyamine Polymers

(c)(1). Synthetic polysaccharides consisting partly or entirely of aminosugars bound by beta-1,2, beta-1,3, beta-1,4 and/or beta-1,6 linkages may be regarded as non-absorbable potential carbonyl trapping agents.

(c)(2). Mixed polysaccharide polymeric derivatives. Primary amine, aminoalkyl (one to ten carbons per alkyl group), amino-hydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidinyl-alkyl (one to ten carbons per alkyl group), aminoalkyl-guanidinyl (one to ten carbons per alkyl group), guanidine,

aminobenzene and aminoalkylbenzene (one to ten carbons per alkyl group) functional groups may be covalently attached to matrices such as epi-chlorohydrin copolymers of cellulose or chitin. Functional group spacer groups may include alkene as well as alkyl groups.

(c)(3). Non-polysaccharide polymeric derivatives. Primary amine, aminoalkyl (one to ten carbons per alkyl group), amino-hydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidinylalkyl (one to ten carbons per alkyl group), aminoalkyl-guanidinyl (one to ten carbons per alkyl group), guanidine, aminobenzene and aminoalkylbenzene (one to ten carbons per alkyl group) functional groups may be covalently attached to a wide variety of synthetic non-digestible polymers. Functional group spacer groups may include alkene as well as alkyl groups. Like their sugar-based counterparts, these agents should be capable of reacting with dietary carbonyl compounds. Nitrogen-containing functional groups may be covalently attached to synthetic supports such as polystyrene, styrene-divinylbenzene copolymer, polyvinyl alcohol and crosslinked derivatives thereof.

(v) Co-Administration of Antioxidants and Lipid Peroxidation Inhibitors

It is claimed that the therapeutic value of the primary agents described herein may be maximized by administration in conjunction with recognized antioxidant free radical trapping compounds such as vitamin E (Stuckey, 1968, pp. 214-215) or other agents previously recognized as adjuncts which facilitate in vivo capability to inhibit lipid peroxidation, such as selenium (Stuckey, 1968, pg. 236). Citric acid may also be included in this category of co-administered agents, as it is recognized as having antioxidant properties (Budavari and coworkers, 1989, pg. 363). This agent is also recognized as an inhibitor of Maillard reactions (Stuckey, 1968, pg. 210). In a published list of agents which function to supplement the chain-breaking antioxidant property of vitamin E, Tappel (1970, pg. 1138) mentioned

ubiquinol, seleno-amino acids and sulfhydryl compounds (such as, glutathione, sulfhydryl proteins and methionine). Butylated-hydroxytoluene (Frankel, 1987, pg. 81) and beta-carotene (Frankel, 1987, pg. 82) should also be included in this group.

(vi) Prophylactic Vitamin Co-Administration

It is yet still another object of this invention that the safety and effectiveness of the products described herein may be optimized by co-administration of vitamins and derivatives thereof which may be inadvertently depleted by the therapeutic treatment of this invention or by the etiology of the disease being addressed, such as vitamin A (retinol), vitamin A aldehyde (retinal), vitamin A acid (retinoic acid), vitamin B₁ (thiamine), vitamin B₂ (riboflavin), vitamin B₆ (pyridoxine), vitamin B₁₂ (cyanocobalamin), vitamin D₂, vitamin D₃, vitamin H (biotin), vitamin K₁, vitamin K₁ oxide, vitamin(s) K₂, vitamin K₅ and vitamin K₆, vitamin K₇, vitamin K-S(II), vitamin L₁, vitamin L₂, vitamin U, alpha-carotene, beta-carotene, gamma-carotene, omega-carotene, carnitine (vitamin B₇), folic acid (vitamin B_c), folinic acid, niacinamide, nicotinic acid, pantothenic acid, pyridoxal, pyridoxal 5-phosphate, and pyridoxamine.

(vii) Co-Administration of Metabolites at Risk of Depletion

It is another object of this invention that the safety and effectiveness of the products described herein may be optimized by co-administration of other metabolites, such as glycine, which may be depleted within the body during long term drug use. As many of the absorbable amine drugs described herein are excreted from the body as glycine conjugates, co-administration of glycine may be advisable. Coenzyme A is a required cofactor for hippuricase, the liver enzyme which adds glycine to benzoic acid derivatives. Activity of hippuricase in glycinating some of the absorbable carbonyl-trapping drugs described herein may sequester a disproportionate fraction of the endogenous coenzyme A pool. Hence co-administration of pantothenic acid, a

metabolic precursor of coenzyme A, may also serve to optimize the therapeutic procedures described herein.

(viii) Co-Administration of Sulfhydryl Agents

Noting the well documented ability of carbonyl agents to react with sulfhydryl groups (Jellum and coworkers, 1973), it is a further object of this invention that methionine and homocysteine may also be of clinical benefit as absorbable drugs capable of covalently binding aldehyde or ketone agents. It is also claimed that these drugs can be used most effectively when administered in conjunction with absorbable and non-absorbable amine and amine-related drugs described herein. Homocysteine contains a free sulfhydryl group. Methionine is converted in vivo to homocysteine by several enzymatic reactions which remove a methyl group. Thioctic acid, also known as alpha-lipoic acid, is also included in this category, as its structure includes a disulfide group. This agent, a recognized growth factor (Budavari and coworkers, 1989, pg. 1469), may tend to be depleted in the tissues of patients having chronic inflammatory diseases involving etiologies which include dysfunction of aldehyde and/or ketone metabolism. The ability of acetaldhyde to combine with thioctic acid, thus deactivating it, has been reported (Smith, 1976, pg. 195). Hence the inclusion of thioctic acid in pharmaceutical preparations such as those described herein may be of clinical benefit.

(ix) Factors Affecting Daily Dosage Schedule

A daily protocol of amine and amine-related drug consumption, in combination with co-agents defined herein, may be defined such that drug products are administered in timed-release and/or color coded tablets or capsules, so as to facilitate patient compliance and maximize therapeutic value.

(4) Therapeutic Utilization

Although their primary etiologies remain to be determined, prior

art information indicates that the secondary etiological processes of degenerative diseases such as rheumatoid arthritis depends, in part, on chronic inflammation. In addition, evidence of increased lipid peroxidation has been demonstrated in studies on muscular dystrophy and multiple sclerosis (Halliwell and Gutteridge, 1985, pg. 125).

Two examples may serve to illustrate the practical application of this invention.

Example One: Pearson and Shaw (1982, pg. 299) described the following summary of an arthritis patient taking vitamin E and vitamin A:

The correct dose of antioxidants for effective arthritis therapy must be determined by experimentation. The effective dose may be quite high. For example, a friend of ours who is a well-known artist in his fifties developed arthritis in his hands. This man's hands became so painful and stiff he could no longer use his fingers to remove the caps from his tubes of paint. He tried vitamin E at increasing dose levels. It was not until he got up to 10,000 I.U. of E and 20,000 I.U. of A per day that he obtained relief from the pain and crippling stiffness. His hands are now flexible and can be used to draw without difficulty. But they remain so only as long as our friend takes 10,000 I.U. of E and 20,000 I.U. of A a day, not less (he's tried).

This dosage of vitamin E far exceeds presently accepted levels of daily usage, which are generally regarded as being in the range of 400 I.U. per day. This particular combination of vitamins E and A, both lipophilic, would not be expected to inhibit any of the free radical reactions taking place in aqueous micro-environments. Nor would it chemically bind and thus deactivate any reactive aldehydes generated by the inflammatory process, as such aldehydes are water soluble.

Example Two: Patient L.S. has a history of arthritis dating back to a serious automobile accident in 1980. By January of 1991 she had serious arthritic involvement of the lumbar spine and chronic hip and knee joint pain on a continuous basis. She had difficulty raising herself from a chair, required the assistance of a cane for activities as simple as walking from her front door to her car, was no longer able to go up or down a flight of stairs, and required use of a prescription analgesic drug every two hours during the night to sleep. She had participated in a program at the Pain Clinic of the University of Miami Medical School and at doctor's advice had used prescription drugs which included *Clinoril* (R) and *Anaprox* (R), both non-steroidal anti-inflammatory agents. At the recommendation of this inventor, patient L.S. began taking 800 I.U. vitamin E, 1. gm of methionine and 1.1 gm PABA per day for two months. Subsequently, vitamin E and methionine usage remained the same and PABA usage was increased to 2.2 gm per day, with the protocol continued on an indefinite basis.

When previously examined by an orthopedics physician a diagnosis was established which included:

...Lumbar spine X-Rays in AP and lateral views show extensive degenerative arthritic changes at multiple levels of the lumbar spine...severe arthritic changes lumbar spine. Bursitis left greater trochanter clinically...She will always have a problem related to her underlying degenerative disease involving her lower back...She is favoring her left leg...Her straight leg raising is limited on the left side...

Ten weeks after initiating this inventor's PABA/vitamin E/methionine protocol, patient L.S. reported that her arthritis-related pain was much decreased and her functional status much improved. By four months into use of this therapeutic protocol patient L.S. had stopped using her cane, had a walking gait which was much improved, had taken to raking leaves in the yard as a form of exercise, and no longer required nighttime

analgesics to sleep. At twelve months on this protocol, patient L. S. reported climbing and descending a flight of stairs without difficulty, and her ability to climb stairs has continued to improve. When re-examined by her orthopedics physician seven months after beginning therapy, who was not informed of her use of the PABA/vitamin E/methionine protocol, the doctor noted, in part:

This patient is markedly better. She has normal straight leg raising. She has no significant leg pain. She walks well on her toes and walks well on her heels now without any evidence of motor weakness. There is no limp present.

Unaware of the patient's collaborative effort with this inventor, the orthopedics physician was unable to provide an explanation of the marked improvement in the clinical status of patient L.S. At her office visit patient L. S. noted that she had stopped taking *Anaprox*, which her orthopedics physician had prescribed seven months earlier.

This inventor recognizes the novel and original composition of primary amine and amine-related benzoic acid derivatives as primary agents to be used with known antioxidant free radical trapping or inhibiting co-agents and not including vitamin C beyond its United States recommended daily allowance as a type of composition likely to have increased, synergistic properties for the treatment of chronic inflammatory diseases. This inventive strategy and the compositions thereof for clinical treatment of these diseases has not been previously recognized.

PABA, many of the other amine and amine-related primary agents, as well as the antioxidant free radical trapping co-agents are chemicals which have been previously synthesized and described. Yet the present invention recognizes a new and novel combination of therapeutic properties, never recognized previously by people trained in this field, and the clinical applications thereof. This invention constitutes a significant and practical advance-

ment of the clinical therapeutic technology available for treating chronic inflammatory diseases.

Without further elaboration the foregoing will so fully illustrate my invention that others may, by applying current or future knowledge, adapt the same for use under various conditions of service.

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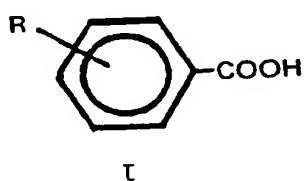
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I claim:

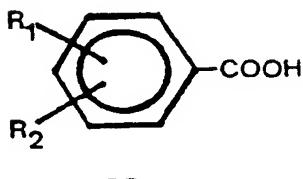
1. Use of a composition comprising a therapeutically effective amount of a primary agent and at least one co-agent, said primary agent comprising a water soluble, low molecular weight primary amine or amine-related derivative of benzoic acid in the molecular weight range of 100 to 1,400, for use in the treatment of symptoms of chronic inflammatory disorders featuring pathology based in part on increased lipid peroxidation, wherein said primary and co-agent combination produces an anti-inflammatory and analgesic effect.
2. Use of a composition comprising a therapeutically effective amount of a primary agent and at least one co-agent for treatment of the symptomology of a chronic inflammatory disease, wherein the chronic inflammatory disease is characterized in part by the deterioration of intracellular and extracellular structures and is characterized by the spurious pathological chemical covalent bond crosslinking of said structures, formation of pathological addition products of said structures, or chemical cleavage products of said structures, said deterioration resulting from reaction of inflammation site structures in the human with disease-induced carbonyl-containing aliphatic and aromatic hydrocarbons resulting from increased lipid peroxidation associated with chronic inflammation.
3. The use of Claim 1 characterized in that the primary agent has at least one primary amine group or amine-related group thereon for reaction with lipid peroxidation product carbonyl groups to decrease the deterioration of said intracellular and extracellular structures and to decrease the spurious pathological chemical crosslinking, other derivation or cleavage of said structures by permitting said primary agent to effectively compete with and covalently bind to said disease-induced carbonyl-containing lipid peroxidation products.
4. The use of Claim 1 characterized in that the primary agent additionally does not interact with normal cell metabolism of

said human or does so in a non-cytotoxic manner, and wherein said primary agent is readily absorbed by the kidney tissue of said human and excreted in the urine of said human without nephrotoxic consequences.

5. Use of Claim 1 characterized in that the primary agent is a water soluble, low molecular weight substance (100 to 1,400 range of molecular weights) selected from the group consisting of the free acid forms, salts, benzene ring isomers, amide derivatives, carboxylic acid ester derivatives and analogous non-aromatic benzene ring derivatives of the group consisting of:



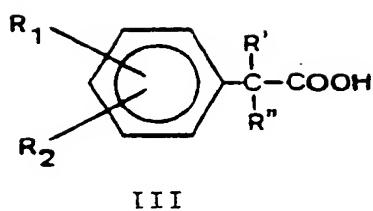
$R = -NH_2$
 -aminoalkyl group having
 1-10 carbons including
 hydrocarbon isomers
 and/or hydroxylated
 derivatives thereof
 $-NHC(=NH)NH_2$
 $-(CH_2)_nNHC(=NH)NH_2$,
 where $n = 1-10$
 $-C(=NH)-NH_2$
 $-(CH_2)_n-CH=NC(=NH)NH_2$,
 where $n = 1-10$
 $-NHC(=NH)NHNH$,
 $-(CH_2)_nNHC(=NH)NHNH$,
 where $n = 1-10$
 $-(CH_2)_n-CH=NC(=NH)NHNH$,
 where $n = 1-10$
 $-NHNHC(=NH)NH_2$
 $-(CH_2)_n-NHNHC(=NH)NH_2$,
 where $n = 1-10$
 $-(CH_2)_n-CH=N-NHC(=NH)NH_2$,
 where $n = 1-10$



$R_1 = -NH_2$
 -aminoalkyl group
 (1-10 carbons)
 including hydrocarbon
 isomers and/or
 hydroxylated
 derivatives thereof
 $-(CH_2)_nNHC(=NH)NH_2$,
 where $n = 1-10$
 $-C(=NH)-NH_2$
 $-(CH_2)_n-CH=NC(=NH)NH_2$,
 where $n = 1-10$
 $-NHC(=NH)NHNH$,
 (continued)

$-(CH_2)_nNHC(=NH)NHNH_2$
 where $n = 1-10$
 $-(CH_2)_n-CH=NC(=NH)NHNH_2$
 where $n = 1-10$
 $-NHNHC(=NH)NH_2$
 $-(CH_2)_n-NHNHC(=NH)NH_2$
 where $n = 1-10$
 $-(CH_2)_n-CH=N-NHC(=NH)NH_2$
 where $n = 1-10$

$R_2 = -NH_2$
 $-OH$
 $-O-CH_3$
 $-O-R'$ with alkyloxy
 group R' having 2-10
 carbons including
 hydrocarbon isomers
 and/or hydroxylated
 derivatives thereof
 $-aminoalkyl$ group
 (1-10 carbons)
 including hydrocarbon
 isomers and/or
 hydroxylated
 derivatives thereof
 $-SO_2H$
 $-CH_3$
 $-(CH_2)_nCH_3$ where $n = 1-10$
 including hydrocarbon
 isomers and/or
 hydroxylated
 derivatives thereof



$R_1 = -(CH_2)_n-NH$, where $n = 0-10$
 including isomers of
 the aminoalkyl group
 and hydroxylated
 derivatives thereof
 $-C(=NH)-NH_2$
 $-NHC(=NH)NH_2$
 $-(CH_2)_nNHC(=NH)NH_2$
 where $n = 1-10$
 $-(CH_2)_n-CH=NC(=NH)NH_2$
 where $n = 1-10$
 $-NHC(=NH)NHNH_2$
 $-(CH_2)_nNHC(=NH)NHNH_2$
 where $n = 1-10$
 $-(CH_2)_n-CH=NC(=NH)NHNH_2$
 where $n = 1-10$
 $-NHNHC(=NH)NH_2$
 $-(CH_2)_n-NHNHC(=NH)NH_2$
 where $n = 1-10$
 $-(CH_2)_n-CH=N-NHC(=NH)NH_2$
 where $n = 1-10$
 (continued)

R_2 = -NH₂
-H
-OH
-O-CH₃
-O-R₃ where alkyl oxy
group R₃ has 2-10
carbons including
hydrocarbon isomers
and/or hydroxylated
derivatives thereof
-aminoalkyl group
(1-10 carbons)
including hydrocarbon
isomers and/or
hydroxylated
derivatives thereof
-SO₂H
-CH₂
-(CH₂)_nCH₃ where n = 1-10
including hydrocarbon
isomers and/or
hydroxylated
derivatives thereof

R' = -H
-CH₃
-OH

R'' = -H
-CH₃
-OH

for controlling the symptoms of disorders selected from the group consisting of chronic gingivitis, chronic periodontitis, chronic autoimmune gastritis, ileitis, colitis, interstitial cystitis, arthritis, tendinitis, carpal tunnel syndrome and other cumulative trauma disorders, systemic lupus erythematosus, autoimmune vasculitis, asbestosis, silicosis, chronic obstructive pulmonary disease, Lyme disease, inflammatory myopathies, status epilepticus, inflammatory neuropathies, myasthenia gravis, multiple sclerosis, as well as lessening of inflammatory site edema, and treatment of post-event ischemia and reperfusion symptomology resulting from acute central nervous system trauma, stroke and myocardial infarction.

6. The use of Claim 1 characterized in that said therapeutically effective amount of said primary agent is a dosage in the range of one gram/day to 20 grams/day.

7. The use of Claim 1 characterized in that said therapeutically effective amount of the primary agent is administered orally.

8. The use of Claim 1 characterized in that said therapeutically effective amount of the primary agent is administered intravenously.

9. The use of Claim 1 characterized in that the co-agent is a non-absorbable polyamine substance or non-absorbable polyamine-related substance, a therapeutically effective amount of said co-agent acting to covalently bind to and sequester dietary carbonyl-containing products in said human for controlling the symptoms of disorders selected from the group consisting of chronic gingivitis, chronic periodontitis, chronic autoimmune gastritis, ileitis, colitis, interstitial cystitis, arthritis, tendinitis, carpal tunnel syndrome and other cumulative trauma disorders, systemic lupus erythematosus, autoimmune vasculitis, asbestosis, silicosis, chronic obstructive pulmonary disease, Lyme disease, inflammatory myopathies, status epilepticus, inflammatory neuropathies, myasthenia gravis, multiple sclerosis, as well as lessening of inflammatory site edema, and treatment of post-event ischemia and reperfusion symptomology resulting from acute central nervous system trauma, stroke and myocardial infarction.

10. The use of Claim 9 characterized in that the co-agent is a non-absorbable polyamine substance or non-absorbable polyamine-related substance selected from the group consisting of:

- a. naturally occurring polysaccharides having beta-1,2, beta-1,3, beta-1,4 and/or beta-1,6 linkages containing aminosugars including the chitin class of biopolymers having the general structure of poly-beta-(1→4)-N-acetyl-D-glucosamine, and bearing at least one free primary amine group;
- b. deacetylated naturally occurring polysaccharides, having at least one N-acetylated residue, including chitosan, deacetylated chondroitin sulfate, or deacetylated hyaluronic acid;
- c. chemically aminated polysaccharides selected from the group consisting of:

aminodeoxy polysaccharides such as 2-amino-2-deoxy-cellulose; aminoalkyl-, amino(hydroxyalkyl)-, aminoalkyl-ether-, and amino(hydroxyalkyl)-ether- derivatives of cellulose, chitin and other naturally occurring non-digestible carbohydrates selected from the group consisting of

$\text{H}_2\text{N}-(\text{CH}_2)_n-\text{[carbohydrate]}$ where $n = 1-10$, including alkyl isomers;

$\text{H}_2\text{N}-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $m = 0-10$ and $n = 0-10$;

$\text{H}_2\text{N}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$ where $n = 1-10$;

$\text{H}_2\text{N}-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$ where $m = 0-10$ and $n = 0-10$;

aminobenzyl- derivatives of cellulose, chitin or other naturally occurring non-digestible carbohydrates selected from the group consisting of

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{[carbohydrate]}$,

$\text{H}_2\text{N}-\text{CH}_2-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{[carbohydrate]}$,

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$ where $n = 0 - 10$, and

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$ where $m = 0-10$ and $n = 0-10$, including p-, o- and m-benzene ring amino-isomers, aminomethyl- isomers and alkyl group isomers thereof;

guanidine and aminoguanidine derivatives of cellulose, chitin or other naturally occurring non-absorbable carbohydrates selected from the group consisting of:

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{O}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$, where $n = 1-10$, in-

cluding hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{O- [carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{NH- [carbohydrate]}$;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{NH}-\text{(CH}_2\text{)}_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{NH}-\text{(CH}_2\text{)}_n-\text{O- [carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NHC}(=\text{NH})-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{O- [carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH-NH- [carbohydrate]}$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH-NH}-\text{(CH}_2\text{)}_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH-NH}-\text{(CH}_2\text{)}_n-\text{O- [carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH-N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH-N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{O- [carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

d. primary amine, aminoguanidine and guanidine derivatives of sucrose polyesters having one or more carbonyl trapping functional group per molecule wherein each carbonyl trapping

functional group is in the omega-, omega-1 or other isomeric position within the fatty acyl chains, wherein each fatty acyl chain may have from 3 to 26 carbons, from one to five nitrogen functional groups and from one to 24 hydroxyl groups;

c. synthetic polysaccharides consisting partly or entirely of aminosugars bound by beta-1,2, beta-1,3, beta-1,4 and/or beta-1,6 linkages;

f. mixed polysaccharide polymeric derivatives wherein primary amine, aminoalkyl (one to ten carbons per alkyl group), aminohydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidinylalkyl (one to ten carbons per alkyl group), aminoalkylguanidinyl (one to ten carbons per alkyl group), guanidine, aminobenzene and/or aminoalkylbenzene (one to ten carbons per alkyl group) functional groups are covalently attached to matrices such as epichlorohydrin copolymers of cellulose or chitin and wherein hydrocarbon spacer groups may include alkene as well as alkyl groups; and

g. non-polysaccharide polymeric derivatives wherein primary amine, aminoalkyl (one to ten carbons per alkyl group), aminohydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidinylalkyl (one to ten carbons per alkyl group), aminoalkylguanidinyl (one to ten carbons per alkyl group), guanidine, aminobenzene and/or aminoalkylbenzene (one to ten carbons per alkyl group) functional groups are covalently attached to a synthetic non-digestible polymer selected from the group consisting of polystyrene, styrene-divinylbenzene copolymer, polyvinyl alcohol and crosslinked derivatives thereof, and wherein hydrocarbon spacer groups may include alkene as well as alkyl groups.

11. The use of Claim 9 characterized in that said co-agent is in a microfibrillated form or microcrystalline form having enhanced surface area, increased porosity, increased water retention capacity and enhanced chemical accessibility.

12. The use of Claim 9 characterized in that said therapeuti-

cally effective amount of said non-absorbable polyamine co-agent or non-absorbable polyamine-related co-agent is administered orally.

13. The use of Claim 9 characterized in that said therapeutically effective amount of said co-agent is a dosage in the range of one gram/day to 40 grams/day.

14. The use of Claim 1 characterized in that at least one co-agent is selected from the group consisting of antioxidants and free radical trapping compounds, chemicals having indirect antioxidant properties, suspending reagents, vitamins and derivatives thereof, chemical conjugating agents which facilitate kidney drug elimination, metabolites at risk of depletion, and sulfhydryl containing chemicals for controlling the symptoms of disorders selected from the group consisting of chronic gingivitis, chronic periodontitis, chronic autoimmune gastritis, ileitis, colitis, interstitial cystitis, arthritis, tendinitis, carpal tunnel syndrome and other cumulative trauma disorders, systemic lupus erythematosus, autoimmune vasculitis, asbestosis, silicosis, chronic obstructive pulmonary disease, Lyme disease, inflammatory myopathies, status epilepticus, inflammatory neuropathies, myasthenia gravis, multiple sclerosis, as well as lessening of inflammatory site edema, and treatment of post-event ischemia and reperfusion symptomology resulting from acute central nervous system trauma, stroke and myocardial infarction.

15. The use of Claim 14 characterized in that said co-agent antioxidants and free radical trapping compounds are selected from the group consisting of vitamin E (alpha-tocopherol), vitamin E acetate, vitamin E succinate, mixed tocopherols, beta-carotene, vitamin A, butylated hydroxytoluene, citric acid, ubiquinol, glutathione, homocysteine and methionine.

16. The use of Claim 14 characterized in that said co-agents having indirect antioxidant properties are selected from the group consisting of selenium and seleno-containing amino acids.

17. The use of Claim 14 characterized in that the co-agent sus-

pending reagents are selected from the group consisting of carboxymethyl cellulose, microcrystalline cellulose, cellulose, starch, dicalcium phosphate, tricalcium phosphate, stearic acid, magnesium stearate, silica, soy flour, watercress, yeast, alfalfa, parselley, lecithin, rice bran, gum tragacanth, gum guar, gum agar, gum arabic, gum carrageenan, gum ghatti, gum karaya, locust bean gum, gum mastic, gum mesquite and gum xanthan, and wherein suspending reagents may be compounded together with a primary agent and at least one co-agent so as to produce a slow release formula.

18. The use of Claim 14 characterized in that said vitamins are selected from the group consisting of vitamin A, vitamin A aldehyde (retinal), vitamin A acid (retinoic acid), vitamin B₁ (thiamine), vitamin B₂ (riboflavin), vitamin B₆ (pyridoxine), vitamin B₁₂ (cyanocobalamin), vitamin D₂, vitamin D₃, vitamin H (biotin), vitamin K₁, vitamin K₁ oxide, vitamin(s) K₂, vitamin K₅ and vitamin K₆, vitamin K₇, vitamin K-S(II), vitamin L₁, vitamin L₂, vitamin U, alpha-carotene, beta-carotene, gamma-carotene, omega-carotene, carnitine (vitamin B₇), folic acid (vitamin Bc), folinic acid, niacinamide, nicotinic acid, pantothenic acid, pyridoxal, pyridoxal 5-phosphate and pyridoxamine.

19. The use of Claim 14 characterized in that said chemical conjugating co-agents which facilitate kidney drug elimination are selected from the group consisting of glycine, derivatives of glycine, and pantothenic acid.

20. The use of Claim 14 characterized in that said metabolite at risk of depletion is selected from the group of co-agents consisting of pantothenic acid and derivatives thereof.

21. The use of Claim 14 characterized in that said co-agent is a sulfhydryl containing agent or derivative thereof such as homocysteine, methionine or thioctic acid (alpha-lipoic acid).

22. The use of Claim 14 characterized in that said at least one

22. The use of Claim 14 characterized in that said at least one co-agent is administered orally.

23. The use of Claim 14 characterized in that said at least one co-agent is administered intravenously.

24. Use of a composition for treating mammals suffering from a chronic inflammatory disorder featuring pathology which includes in part increased lipid peroxidation comprising orally or intravenously administering a therapeutically effective amount of a primary therapeutic agent sufficient to treat said mammal for said mammalian disorder, in combination with at least one co-agent, wherein said mammalian disorder is selected from a group consisting of arthritis, inflammatory site edema, acute central nervous system trauma, stroke and myocardial infarction, wherein the primary therapeutic agent is selected from the group consisting of primary amine and amine-related benzoic acid derivatives which are water soluble and of molecular weight 100 to 1,400 as defined in Claim 5, wherein the primary agent acts by covalently binding to and sequestering carbonyl compounds which result from increased lipid peroxidation in said mammal, and wherein said primary agent is administered with at least one of said co-agents as defined in Claim 9 or Claim 14.

25. The use of Claim 24 characterized in that the primary agent is used in a dosage of from 10 mg/kg/day to 1.0 gm/kg/day.

26. The use of Claim 24 characterized in that the non-absorbable polyamine substance or non-absorbable polyamine-related substance as defined in Claim 9 is used in a dosage of from 10 mg/kg/day to 1.0 gm/kg/day.

27. A pharmaceutical composition for use in the treatment of the symptoms of disorders selected from the group consisting of chronic gingivitis, chronic periodontitis, chronic autoimmune gastritis, ileitis, colitis, interstitial cystitis, arthritis, tendinitis, carpal tunnel syndrome and other cumulative trauma disorders, systemic lupus erythematosus, autoimmune vasculitis,

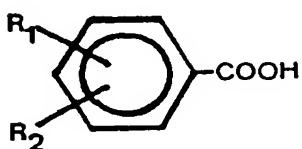
asbestosis, silicosis, chronic obstructive pulmonary disease, Lyme disease, inflammatory myopathies, status epilepticus, inflammatory neuropathies, myasthenia gravis, multiple sclerosis, as well as lessening of inflammatory site edema, and treatment of post-event ischemia and reperfusion symptomatology resulting from acute central nervous system trauma, stroke and myocardial infarction.

the composition comprising a water soluble, low molecular weight primary agent (100 to 1,400 range of molecular weights) selected from the free acid forms, salts, benzene ring isomers, amide derivatives, carboxylic acid ester derivatives and analogous non-aromatic benzene ring derivatives of the group consisting of:



I

$R = -NH_2$
 -aminoalkyl group having 1-10 carbons including hydrocarbon isomers and/or hydroxylated derivatives thereof
 $-NHC(=NH)NH_2$
 $-(CH_2)_nNHC(=NH)NH_2$ where $n = 1-10$
 $-C(=NH)-NH_2$
 $-(CH_2)_n-CH=NC(=NH)NH_2$ where $n = 1-10$
 $-NHC(=NH)NHNH_2$
 $-(CH_2)_nNHC(=NH)NHNH_2$ where $n = 1-10$
 $-(CH_2)_n-CH=NC(=NH)NHNH_2$ where $n = 1-10$
 $-NHNHC(=NH)NH_2$
 $-(CH_2)_n-NHNHC(=NH)NH_2$ where $n = 1-10$
 $-(CH_2)_n-CH=N-NHC(=NH)NH_2$ where $n = 1-10$

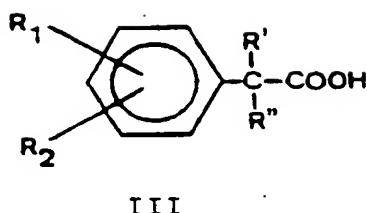


II

$R_1 = -NH_2$
 -aminoalkyl group (1-10 carbons) including hydrocarbon isomers and/or hydroxylated derivatives thereof
 $-(CH_2)_nNHC(=NH)NH_2$ where $n = 1-10$
 $-C(=NH)-NH_2$
 $-(CH_2)_n-CH=NC(=NH)NH_2$ where $n = 1-10$
 (continued)

-NHC(=NH)NNH₂,
 -(CH₂)_nNHC(=NH)NNH₂,
 where n = 1-10
 -(CH₂)_n-CH=NC(=NH)NNH₂,
 where n = 1-10
 -NHNHC(=NH)NH₂,
 -(CH₂)_n-NHNHC(=NH)NH₂,
 where n = 1-10
 -(CH₂)_n-CH=N-NHC(=NH)NH₂,
 where n = 1-10

$R_2 =$ -NH₂
 -OH
 -O-CH₃
 -O-R' with alkyloxy
 group R' having 2-10
 carbons including
 hydrocarbon isomers
 and/or hydroxylated
 derivatives thereof
 -aminoalkyl group
 (1-10 carbons)
 including hydrocarbon
 isomers and/or
 hydroxylated
 derivatives thereof
 -SO₃H
 -CH₃
 -(CH₂)_nCH₃ where n = 1-10
 including hydrocarbon
 isomers and/or
 hydroxylated
 derivatives thereof



$R_1 =$ -(CH₂)_n-NH₂ where n = 0-10
 including isomers of
 the aminoalkyl group
 and hydroxylated
 derivatives thereof
 -C(=NH)-NH₂,
 -NHC(=NH)NH₂,
 -(CH₂)_nNHC(=NH)NH₂,
 where n = 1-10
 -(CH₂)_n-CH=NC(=NH)NH₂,
 where n = 1-10
 -NHC(=NH)NNH₂,
 -(CH₂)_nNHC(=NH)NNH₂,
 where n = 1-10
 -(CH₂)_n-CH=NC(=NH)NNH₂,
 where n = 1-10
 -NHNHC(=NH)NH₂,
 -(CH₂)_n-NHNHC(=NH)NH₂,
 where n = 1-10
 -(CH₂)_n-CH=N-NHC(=NH)NH₂,
 where n = 1-10
 (continued)

R_2 = -NH₂
-H
-OH
-O-CH₃
-O-R₃ where alkyloxy group R₃ has 2-10 carbons including hydrocarbon isomers and/or hydroxylated derivatives thereof
-aminoalkyl group (1-10 carbons) including hydrocarbon isomers and/or hydroxylated derivatives thereof
-SO₂H
-CH₃
-(CH₂)_nCH₃ where n = 1-10 including hydrocarbon isomers and/or hydroxylated derivatives thereof

R' = -H
-CH₃
-OH

R'' = -H
-CH₃
-OH,

in a dosage range of from one gram/day to 20 grams/day, in association with a pharmaceutically acceptable carrier thereof.

28. The composition of Claim 27 additionally comprising at least one co-agent.

29. A pharmaceutical composition for use in the treatment of the symptoms of disorders selected from the group consisting of chronic gingivitis, chronic periodontitis, chronic autoimmune gastritis, ileitis, colitis, interstitial cystitis, arthritis, tendinitis, carpal tunnel syndrome and other cumulative trauma disorders, systemic lupus erythematosus, autoimmune vasculitis, asbestosis, silicosis, chronic obstructive pulmonary disease, Lyme disease, inflammatory myopathies, status epilepticus, inflammatory neuropathies, myasthenia gravis, multiple sclerosis, as well as lessening of inflammatory site edema, and treatment of post-cvnt ischemia and reperfusion symptomology

resulting from acute central nervous system trauma, stroke and myocardial infarction.

the composition comprising one or more non-absorbable polyamine substance or non-absorbable polyamine-related substance selected from the group consisting of:

- a. naturally occurring polysaccharides having beta-1,2, beta-1,3, beta-1,4 and/or beta-1,6 linkages containing aminosugars including the chitin class of biopolymers having the general structure of poly-beta-(1→4)-N-acetyl-D-glucosamine, and bearing at least one free primary amino group;
- b. deacetylated naturally occurring polysaccharides, having at least one N-acetylated residue, including chitosan, deacetylated chondroitin sulfate, or deacetylated hyaluronic acid;
- c. chemically aminated polysaccharides selected from the group consisting of:

aminodeoxy polysaccharides such as 2-amino-2-deoxy-cellulose;

aminoalkyl-, amino(hydroxyalkyl)-, aminoalkyl-ether-, and amino(hydroxyalkyl)-ether- derivatives of cellulose, chitin and other naturally occurring non-digestible carbohydrates selected from the group consisting of

$\text{H}_2\text{N}-(\text{CH}_2)_n-\text{[carbohydrate]}$ where $n = 1-10$, including alkyl isomers;

$\text{H}_2\text{N}-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $m = 0-10$ and $n = 0-10$;

$\text{H}_2\text{N}-(\text{CH}_2)_n-\text{O-[carbohydrate]}$ where $n = 1-10$;

$\text{H}_2\text{N}-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{O-[carbohydrate]}$ where $m = 0-10$ and $n = 0-10$;

aminobenzyl- derivatives of cellulose, chitin or other naturally occurring non-digestible carbohydrates selected from the group consisting of

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{[carbohydrate]}$,

$\text{H}_2\text{N}-\text{CH}_2-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{[carbohydrate]}$,

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_n-\text{O-[carbohydrate]}$ where $n = 0-10$, and

$\text{H}_2\text{N}-\text{C}_6\text{H}_4-(\text{CH}_2)_m-\text{CHOH}-(\text{CH}_2)_n-\text{O-[carbohydrate]}$ where $m = 0-10$ and $n = 0-10$, including p-, o- and m-benzene ring aminoisomers, aminomethyl- isomers and alkyl group isomers thereof;

guanidine and aminoguanidine derivatives of cellulose, chitin or other naturally occurring non-absorbable carbohydrates selected from the group consisting of:

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{O}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{N}=\text{CH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{N}=\text{CH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NH}-\text{C}(=\text{NH})-\text{NH}-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{NH}-\text{C}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NH}-\text{C}(=\text{NH})-\text{NH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NH}-\text{C}(=\text{NH})-\text{N}=\text{CH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{NH}-\text{C}(=\text{NH})-\text{N}=\text{CH}-(\text{CH}_2)_n-\text{O}-\text{[carbohydrate]}$, where $n = 1-10$, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{NH}-\text{[carbohydrate]}$;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{NH}-(\text{CH}_2)_n-\text{[carbohydrate]}$, where $n = 1-10$,

including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{NH}-\text{(CH}_2\text{)}_n-\text{O}-[\text{carbohydrate}]$, where n = 1-10, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-[\text{carbohydrate}]$, where n = 1-10, including hydrocarbon isomers and hydroxylated derivatives thereof;

$\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-\text{N}=\text{CH}-\text{(CH}_2\text{)}_n-\text{O}-[\text{carbohydrate}]$, where n = 1-10, including hydrocarbon isomers, ether linkage isomers and hydroxylated derivatives thereof;

d. primary amine, aminoguanidine and guanidine derivatives of sucrose polyesters having one or more carbonyl trapping functional group per molecule wherein each carbonyl trapping functional group is in the omega-, omega-1 or other isomeric position within the fatty acyl chains, wherein each fatty acyl chain may have from 3 to 26 carbons, from one to five nitrogen functional groups and from one to 24 hydroxyl groups;

e. synthetic polysaccharides consisting partly or entirely of aminosugars bound by beta-1,2, beta-1,3, beta-1,4 and/or beta-1,6 linkages;

f. mixed polysaccharide polymeric derivatives wherein primary amine, aminoalkyl (one to ten carbons per alkyl group), amino-hydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidinylalkyl (one to ten carbons per alkyl group), aminoalkyl-guanidinyl (one to ten carbons per alkyl group), guanidine, aminobenzene and/or aminoalkylbenzene (one to ten carbons per alkyl group) functional groups are covalently attached to matrices such as cpi-chlorohydrin copolymers of cellulose or chitin and wherein hydrocarbon spacer groups may include alkene as well as alkyl groups; and

g. non-polysaccharide polymeric derivatives wherein primary amine, aminoalkyl (one to ten carbons per alkyl group), amino-hydroxyalkyl (one to ten carbons per alkyl group and one to ten hydroxyl groups per alkyl group), aminoguanidine, aminoguanidinylalkyl (one to ten carbons per alkyl group), aminoalkyl-

guanidinyl (one to ten carbons per alkyl group), guanidine, aminobenzene and/or aminoalkylbenzene (one to ten carbons per alkyl group) functional groups are covalently attached to a synthetic non-digestible polymer selected from the group consisting of polystyrene, styrene-divinylbenzene copolymer, polyvinyl alcohol and crosslinked derivatives thereof, and wherein hydrocarbon spacer groups may include alkene as well as alkyl groups.

in a dosage range of from one gram/day to 40 grams/day, in a microfibrillated form or microcrystalline form having enhanced surface area, increased porosity, increased water retention capacity and enhanced chemical accessibility, and in association with a pharmaceutically acceptable carrier thereof.

30. The composition of Claim 28 characterized in that at least one co-agent is selected from the group consisting of anti-oxidants and free radical trapping compounds, chemicals having indirect antioxidant properties, suspending reagents, vitamins and derivatives thereof, chemical conjugating agents which facilitate kidney drug elimination, metabolites at risk of depletion, and sulphhydryl containing chemicals.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/06167

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 31/74, 31/195, 31/19; A01N 37/10, 37/12, 37/44; C07C 229/00

US CL : 424/78.05; 514/567, 568, 570; 562/433, 458

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/78.05; 514/567, 568, 570; 562/433, 458

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, MEDLINE, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 3,956,504 (Sawyer) 11 May 1976, see entire document.	1-30
Y	US, A, 4,584,379 (Wagner) 22 April 1986, see entire document.	1-30
Y	US, A, 4,017,623 (Giudicelli et al.) 12 April 1977, see entire document.	1-30
Y	US, A, 3,926,961 (Ferrini et al.) 16 December 1975, see entire document.	1-30
Y	US, A, 4,851,426 (Ladkani et al.) 25 July 1989, see entire document.	1-30

 Further documents are listed in the continuation of Box C.

See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

20 September 1993

Date of mailing of the international search report

29 SEP 1993

Name and mailing address of the ISA/US
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/06167

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Physicians' Desk Reference, Edition 45, issued 1991, page 1045, see entire document.	1-30
Y	Biochemical Pharmacology, Volume 38, No. 8, issued 1989, Lehmann et al., "Substrates for arachidonic acid co-oxidation with peroxidase/hydrogen peroxide", pages 1209-1216, see entire document.	1-30

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